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Effects of whole-body vibration training on lower-limb motor function and neural plasticity in stroke patients: protocol for a randomized controlled clinical trial

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ABSTRACT

Introduction Lower-limb motor dysfunction is very common in stroke patients, and usually caused by brain neural connectivity disorder. Recent studies have shown that whole-body vibration training (WBVT) significantly improves lower-limb motor function in stroke patients, and may promote nerve remodeling. The purpose of this study is to investigate the effects of WBVT on lower-limb motor function and neuroplasticity in stroke patients.

Methods A single-blind randomized controlled trial will be conducted. Sixty stroke patients will be recruited and allocated randomly to WBVT, routine rehabilitation training (RRT), and control groups. The WBVT and RRT interventions will be implemented as five 25-min sessions per week for 12 weeks; the control group will receive no exercise intervention. Transcranial magnetic stimulation will be used to assess neural plasticity, and lower-limb motor function will be assessed using indicators of strength, walking ability, and joint activity. Assessments will be conducted at baseline, 6 weeks, and 12 weeks, and at 4 and 8 weeks after intervention completion.

Ethics and dissemination This study has been approved by the Shanghai University of Sport Research Ethics Committee (102772021RT067) and will provide data on the effects of WBVT relative to RRT in terms of the improvement of stroke patients' lower-limb motor function and neural plasticity. The results of this study can provide a theoretical basis for the application of WBVT for stroke patients.

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Abbreviations

WBVT	Whole body vibration training
RRT	routine rehabilitation training
MEP	Motor evoked potential
Pre-SMA	pre-supplementary motor area
FMA	Fugl-Meyer assessment
TUG	Time up and go

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Strengths and limitations of this study

1. Because it is a sports intervention, the safety of the stroke patients during exercise is worth worrying about.
2. How to select and control participants in a longitudinal study is one of the difficulties of this project.
3. The patients will come from one geographic area which limits the generalisability.

INTRODUCTION

Stroke is prevalent and associated with high disability, recurrence, and mortality rates.[1] The latest global burden of disease study shows that the overall lifetime risk of stroke in China is 39.9%, ranking first in the world, Stroke is also the leading cause among diseases of lost years of life in China.[2] Stroke patients often have a variety of sequelae. The most common is hemiplegia, which is characterized by numbness and weakness of one limb and continuous increases in muscle tension, which significantly reduce patients' ability to perform daily activities and quality of life.[3] Lower-limb function can be restored only to a certain extent in more than 70% of hemiplegic patients, and most such patients cannot obtain a good gait or walking speed.[4] Lower-limb motor dysfunction after stroke is caused by central nervous system injury and results in abnormal movement patterns.[5] Its main characteristics are poor muscle strength,[6] spasm,[5] joint instability,[7] combined reactions,[8] and joint movement.[9] Thus, the improvement of affected patients' muscle strength, balance, and walking ability is key to the improvement of their lower-limb motor function.

Neural plasticity generally refers to the nervous system's inherent ability to make structural and functional changes to adapt to changes in the internal and external environments .[10] Changes in neural plasticity after stroke have been shown to be the basis for the recovery of motor function.[11] After unilateral stroke, neural plasticity includes two aspects: 1) changes in neural synaptic connections and 2) changes in the excitability of various structures. Functional recovery after stroke is related to changes in the brain's anatomical structure and function, in the motor cortex and other regions.[12] The presence of lesions on one side of the cerebral hemisphere reduces or inhibits the excitability of the motor cortex on that side[13], and improvement of this excitability is key to rehabilitation. The primary motor cortex (M1) provides the main output to the descending motor system and autonomous motor commands, and is linked closely to somatosensory and spatial processing in the parietal lobe, premotor cortex, and auxiliary motor area; thus, changes in its excitability alter motor function[14]. M1 is also defined as the scalp site where the minimum stimulation intensity causes the maximum motor evoked potential (MEP) of the muscle. Thus, changes in the MEP reflect motor function[15]. The pre-supplementary motor area (pre-SMA), located between the prefrontal lobe and motor system, is responsible for language and idea generation, action recognition, working memory maintenance, learning, and the execution of action sequences, among other functions[16]. The enhancement of pre-SMA activity has been found to alleviate M1 disorder in stroke patients, and changes in connectivity between motor areas may contribute to the improvement of motor function in these patients[17]. Thus, the recovery of limb motor function in stroke patients is related to the functional connectivity between cerebral hemispheres and the normalization of the bilateral sensorimotor cortical network.

Exercise intervention therapy has the advantages of high compliance, minimal side effects, and strong operability. It has become an important means of rehabilitation for stroke patients[18]. Functional recovery after stroke is a complex process, and repeated sensory input is among the most effective means of improving the cortical structure and body function [19]. The repeated performance of specific actions during physical exercise has been found to establish motor memory, which is a form of brain plasticity improvement[20]. Thus, in addition to improving muscle strength and joint activity, exercise intervention therapy can aid the recovery of neural plasticity and brain function, thereby promoting the recovery of motor function[21]. However, after the acute phase of stroke, patients have limited active motor ability and their executive function is affected to a certain extent; these factors make it difficult for them to skillfully remember and perform complex and diverse rehabilitation actions, which may hinder the effectiveness of rehabilitation exercise[22]. Thus, the key to effective rehabilitation is to give patients greater motor stimulation within their limited range of activities.

As a passive training method, whole-body vibration training (WBVT) involves the generation of mechanical waves through a training platform to stimulate muscle vibration and neuromuscular regulation and adaptation[23]. It has also been found to effectively improve the lower-limb muscle strength[24], spasm[25], walking ability[26], and balance[27] of many people, including stroke patients. A review of the clinical application of WBVT in patients with chronic stroke showed that its main effects include the reduction of spasm, promotion of muscle contraction, stimulation of the proprioceptive system, and improvement of motor control ability [28]. WBVT has also been shown to increase oxygen consumption and promote the release of vasodilators in stroke patients, without additional effects on the heart rate or blood pressure[29]. Thus, a period of such training can improve blood perfusion on the affected side in stroke patients, thereby alleviating muscle tension, eliminating spasm, and improving balance and walking ability [30]. In addition, a transcranial magnetic stimulation (TMS) study revealed significant changes in cortical excitability after vibration training in healthy people[31]. The convergence of evidence from several experimental studies suggests that WBVT induces the reorganization of sensory motor processes in the brain in healthy people[24]. It may also promote functional recovery after stroke by enhancing the proprioceptive afferents of the central nervous system, inducing cortical and subcortical reorganization based on the rebalancing and shaping of cortical and subcortical sensory motor representations[24]. However, the authors of that study believe that WBVT is more suitable for patients who have experienced acute or subacute stroke than for those with chronic stroke. Marconi et al.[32] found that repeated muscle vibration reduced muscle tension and improved motor function on the affected side in stroke patients. TMS revealed that the motor thresholds of these patients decreased, their MEP amplitudes increased, and their flexor muscle activation improved.[32] Thus, the authors concluded that changes in cortical excitability are related to motor function, and that WBVT is a suitable non-drug treatment even after lengthy illness to promote the recovery of neural plasticity and motor function in stroke patients.[32] Thus, WBVT can effectively improve the motor function of stroke patients, and may also have a strong effect on brain neural plasticity. However, little research on this topic has been conducted, and researchers have reached different conclusions. In addition, the vibration training types and parameters that are effective in this context have not been identified; further research is needed.

In sum, little research has examined the application of WBVT for the rehabilitation of stroke patients, and especially the impact of WBVT on these patients' brain function. Thus, this randomized controlled trial (RCT) was designed to examine the effect of

WBVT on stroke patients' lower-limb motor function and neural plasticity. Isokinetic muscle strength will be measured to examine changes in lower-limb muscle strength, and TMS will be used to examine changes in neural plasticity. Changes in secondary outcomes, such as patients' walking ability, balance, and quality of life, will also be assessed. We will compare the effect of WBVT with that of routine rehabilitation training, and observe differences in effect maintenance between these methods.

AIMS AND OBJECTIVES

We aim to determine the effect of 12 weeks of WBVT on stroke patients' lower-limb motor function and neural plasticity, and explore the difference between wbvt and routine rehabilitation training after 6 and 12 weeks of training. In addition, we will evaluate and compare it after 4 and 8 weeks of stopping training. We will also assess the feasibility of a future full-scale RCT.

The study objectives are to:

1. clarify the effects of WBVT on stroke patients' lower-limb motor function and neural plasticity;
2. analyze the training effects and maintenance times of the two training methods;
3. explore the facilitators, barriers, and contextual factors influencing the implementation of WBVT; and
4. test the acceptability of the data collection procedures used.

METHODS AND DESIGN

Study design

This study was designed as a prospective single-blind RCT. Eligible participants with stroke will be assigned randomly to the whole-body vibration training group (WBVG), routine rehabilitation training group (RRTG), and control group (CG) at a ratio of 1:1:1. The WBVG and RRTG will receive exercise interventions in the Sports Laboratory of Shanghai University of Sport, Shanghai, China. The CG will maintain their routine daily lives. The interventions will be implemented 5 times a week for 12 weeks. Participants will be evaluated at baseline, after 6 and 12 weeks of intervention, and 4 and 8 weeks after intervention termination (Figure 1). This research protocol has been approved by the research ethics committee of Shanghai University of Sport (no. 102772021RT067).

Figure 1. Diagram of study flow.

Participants

Participants in Shanghai will be recruited through community outreach, from outpatient clinics, with media advertising, and by telephone. All participants will follow their routine medication and physical therapy/massage regimens during the study period. They will provide written informed consent before inclusion in the study. Before and after the intervention, data on participants' demographic and clinical characteristics will be collected and analyzed (Table 1).

Table 1. Demographic and clinical characteristics of participants

	WBVG	RRTG	CG
Age			
Gender			
Height			
eight			
Time of illness			
Stroke type			
Affected side			
Whether auxiliary equipment is used			
FMA score			
Berg score			
TUGT			
MoCA score			
SF-36			

Note： WBVG， Whole body vibration training group； RRTG， routine rehabilitation training group；CG，control group

Inclusion and exclusion criteria

The inclusion criteria will be: 1) clinical diagnosis of first ischemic or hemorrhagic stroke, 2) Brunnstrom stage IV, 3) ability to stand and walk without the help of another person, 4) stable medical condition, 5) duration of illness ≥ 3 months and 7 ） no vibration training experience. The exclusion criteria will be: 1) diagnosis of transient ischemic attack or subdural or epidural hemorrhage; 2) other nervous system disease; 3) severe skeletal muscle or cardiovascular disease; 4) severe lumbar disc herniation; 5) dysfunction or failure of the heart, lung, liver, kidney, or other major organ; 6) other serious disease or exercise contraindication; and 7) vibration training experience.

Sample size

The sample size has been estimated using the G*power statistical software (version 3.1.9.2 for Windows 7 X64; Franz Faul, Kiel University, Germany), used widely for this purpose. In this part of the study, the sample size was estimated by F tests: analysis of variance (ANOVA): related measures, between factors: computer required sample size. Under the significance level of 0.05 and repeated-measures ANOVA setting of 80% efficacy, the total number of subjects needed was determined to be 42 (14 per group). Considering a 20% loss rate, we plan to recruit 60 subjects (20 per group).

Randomization

Numbers (1–60) will be assigned to the participants according to their recruitment times in an Excel software database, and then a random sequence will be generated using the "= rand ()" formula. This sequence will be sorted to allocate the participants to the study groups. These tasks will be completed by professional computer workers blinded to recruitment and allocation after the completion of recruitment.

Interventions

WBVT intervention

Because the participants will be ill and weak, they will better accept low-frequency vibration training[33], which has been shown to be more likely to induce changes in brain nerve excitation[**Error! Bookmark not defined.**]. The WBVT intervention will be implemented using a platform (I-vib5050A; Bodygreen, Taiwan) that generates vertical vibrations and has an adjustable frequency range (6–12 Hz) with corresponding preset amplitudes. The vibration frequency will be increased in a stepwise manner in three phases (weeks 1–4, 5–8, and 9–12) over the 12-week intervention period. The training will consist of adaptation to the vibration (6, 7, and 7 Hz, respectively, in phases 1–3) with 5 minutes of static standing, 1 minute of rest, two rounds of 5 minutes of rhythmic half-squat to standing practice (alternation of 60° knee flexion and standing for 5 seconds each) with vertical vibration (8, 10, and 12 Hz, respectively, in phases 1–3) and 1 minute rest between rounds, 5 minutes of vertical vibration (8, 10, and 12 Hz, respectively, in phases 1–3) under traction created by the placement of a ~4-cm-thick towel under the front sole of the foot to bend the patient's ankle back and pull the calf muscles with 1 minute rest between rounds, and a final 5 minutes of standing with vibration (6, 7, and 7 Hz, respectively, in phases 1–3). The amplitude will be maintained at 2 mm in all phases. The participants will be monitored continuously during training, and training will be terminated immediately upon complaint of any abnormal condition, such as panic, chest tightness, dizziness, or pain (Table 2).

Table 2. Vibration training schedule

Time	Vibration time （min）	Schedule（min）	Vibration frequency （Hz）
Phase I			
Week 1 and 2	25	5-5-5-5-5	6-8
Week 3 and 4	25	5-5-5-5-5	6-8
Phase II			
Week 5 and 6	25	5-5-5-5-5	7-10
Week 7 and 8	25	5-5-5-5-5	7-10
Phase III			
Week 9 and 10	25	5-5-5-5-5	7-12
Week 11 and 12	25	5-5-5-5-5	7-12

Routine rehabilitation exercise intervention

The routine rehabilitation exercise intervention will consist of in-situ alternate leg lifting with the feet at shoulder width (while in a safe, stable position and with the help of both hands/arms), in-situ squatting (to 60–90°, increasingly gradually according to the patient’s condition) with the feet at shoulder width (while holding a protective rod), in-situ heel lifting while on a step with the feet at shoulder width (while holding a protective rod), and walking on a treadmill equipped with safety handrails (Table 3). As the participants will be ill and weak, their exercise intensity will be monitored using the Borg scale (Table 4)[34].

Table 3. Routine rehabilitation training

Phase	Exercise	Repetitions/duration
I: weeks 1–4		
	Alternating in-situ leg lifts	2 rounds of 30 s, inter-round interval to complete recovery
	In-situ squats	2 rounds of 8–10 repetitions, inter-round interval to complete recovery
	Step heel lifts	2 rounds of 15 repetitions, inter-round interval to complete recovery
	Walking	5 min
II: weeks 5–8		
	Alternating in-situ leg lifts	3 rounds of 30 s, inter-round intervals to complete recovery
	In-situ squats	3 rounds of 8–10 repetitions, inter-round intervals to complete recovery
	Step heel lifts	3 rounds of 15 repetitions, inter-round intervals to complete recovery
	Walking	10 min
III: weeks 9–12		
	Alternating in-situ leg lifts	3 rounds of 30 s, inter-round intervals to complete recovery
	In-situ squats	4 rounds of 8–10 repetitions, inter-round intervals to complete recovery
	Step heel lifts	4 rounds of 15 repetitions, inter-round intervals to complete recovery
	Walking	10 minutes

Table 4. Borg scale

Level	Description

6	No exertion at all
7	Extremely light
8	Light
9	Very light (easy, slow walking at a comfortable pace)
10	This is the effort level where you can’t hear your breath
11	You are able to easily talk and you can run at this level for a long time
12	Light (you are building aerobic endurance)
13	Somewhat hard (you are making quite an effort; you feel tired but can continue)
14	You start to hear your breath, but are not gasping for air
15	You can talk, but it is more challenging, you use one- or two-word answers
16	Hard (this is considered to be your steady state)
17	Very hard (very strenuous and you are very fatigued)
18	Your breathing is vigorous, you can’t talk, you are gasping for air
19	Extremely hard (you are counting the minutes until it ends)
20	Maximal exertion

Table 5. Intervention overview

		Group		
Item no.	Brief name	WBVG	RRTG	CG
1	Why	WBVT	Routine rehabilitation training	Control
2	What	12 weeks training under the guidance of professionals		Maintenance of usual living habits, no regular exercise, regular attendance of health lectures, telephone follow-up
3	What (content)	25 min exercise, five times/week		Attendance of fortnightly health lectures, monthly telephone interviews
4	What (procedure)	Evaluation at baseline ,6 weeks and 12 weeks, and 4 and 8 weeks after intervention termination,reporting of results to participants so that they can understand the physical changes occurring		
5	Who (administrators)	WBVT coach is a professional rehabilitation physician, assessments performed by Shanghai University of Sport PhD students	Routine rehabilitation training coach is a professional rehabilitation physician, assessments performed by Shanghai University of Sport PhD students	Health lectures and telephone interviews performed by Shanghai University of Sport PhD students (College of Physical Education and Training)

6	How	The exercise interventions will take place in a stationary gymnasium, the instructors will direct the whole group face to face		The health lectures will be held in the conference room of the College of Physical Education and Training, Shanghai University of Sport
7	When and how much	See Table 2	See Table 3	Health lectures, 30–50 min; interviews, 10 min
8	How well	Participants will receive regular feedback, including physical and psychological data and reports on their motor skills learning performance; they will be kept up to date on their progress and status to keep them engaged		

WBVG, whole-body vibration training group; RRTG, routine rehabilitation training group; CG,control group;WBVT, whole-body vibration training.

Transcranial magnetic stimulation (TMS) protocol

Electromyographic recording

Surface electromyograms will be recorded from the rectus femoris (RF) muscle with 9-mm-diameter Ag-AgCl surface electrodes. The active and reference electrodes will be placed over the rectus femoris abdominis and above the patella, respectively (Figure 2). The signal will be amplified (1000×), bandpass filtered (2–2.5 kHz; Intronix Technologies Model), digitized at 5 kHz by an analog–digital interface (Micro1401; Cambridge Electronics Design, Cambridge, UK), and saved for offline analysis.

TMS

TMS will be applied to the bilateral M1 with a figure-of-eight–shaped coil (7-cm external loop diameter) connected to two single-pulse monophasic stimulators (Magstim Co., Whitland, Dyfeld, UK). The M1 hotspot will be defined as the scalp location inducing the largest peak–peak MEP amplitude in the contralateral RF muscle. The handle of the test stimulus (TS) coil will be angled posteriorly 30–45° from the midsagittal line. TS1mV will be defined as the lowest TMS intensity required to generate MEPs of 1 mV in the relaxed RF muscle in at least 5 of 10 trials. The resting motor threshold (RMT) will be defined as the lowest TMS intensity required to generate MEPs > 50 V in at least 5 of 10 trials with the target muscle completely relaxed[35].

Figure 2. EMG acquisition site.

Isokinetic strength assessment protocol

Due to the particularities of the participants' conditions, for safety reasons and based on previous isokinetic muscle strength research, the angular velocity for isokinetic strength testing in both lower limbs will 60°/s. The testing instrument will be warmed up and debugged before assessment. The assessment will be performed after an adaptability exercise with the participant's body fixed and his or her hands placed in front of the chest. The test action will be repeated five times with intervening 90-s rest intervals. The average peak torque of the flexor and extensor muscles of the knee joint will be taken as the measure of strength. The peak torque is the gold-standard measure for isokinetic assessment, and has shown high degrees of accuracy and repeatability[36].

Outcomes

Primary outcome

Neural plasticity

MEP amplitude

MEPs will be recorded during TMS. MEP amplitudes will be measured as peak-to-peak values.

Short-interval intracortical inhibition（SICI）

The intensity of the conditioned stimulus (CS) will be 1 mV, the TS intensity will be the RMT, and the interstimulus intervals (ISIs) will be 2, 3, and 4 ms. Before the experiment, the subjects' induced RF 1-mV MEP intensities will be measured as the TS intensities, and the CS intensities will be 80% RMT & 90% RMT. Each block will contain 40 trials in random order.

M1–pre-SMA connectivity

To investigate changes in connectivity between the left M1 and pre-SMA after long-term exercise training, we will perform TMS with two high-power Magstim 200 devices and two figure-of-eight coil sites. Coil placement will be performed as in a similar hemispheric study to avoid overlap[37]. The smaller CS coil will be placed over the right hemisphere to induce a medially directed current in the brain, and will be used to stimulate the pre-SMA. The TS coil will be placed over the leg representation of the left hemisphere for the induction of a posterior–anterior current in the brain. The CS will be delivered by an octagonal coil (50-mm diameter) to stimulate the pre-SMA. Its intensity will be 110% or 90% of the RMT. The angle between the placement direction and the scalp midline will be 45° to induce a front-to-back current[38]. The TS (M1) intensity will be set to evoke a resting MEP with the same TMS coil. The ISIs will be 6, 8, 10, 30, 40, and 50 ms. The strength of the CS will be changed for each block, and complete the order pseudo-random for each subject block. Each block will contain 60 trials. Separate TS will be collected 10 times. The MEP of each ISI will be collected 10 times, for a total of 70 measurements. Each block will contain 70 trials in random order.

Lower-limb motor function

Peak torque

Participants' lower-limb flexion and extension muscle strength will be evaluated using a PHYSIOMED Con-Trex isokinetic testing system at all assessment timepoints.

Brunnstrom stage

The Brunnstrom approach is a set of treatment methods for dyskinesia after central nervous system injury developed by Swedish physiotherapist Signe Brunnstrom. Motor function recovery is divided into six stages, with muscle tension increasing gradually from low to high and joint reaction, joint movement, and spasm gradually becoming significant. With the completion of common motion, separation motion, and fine motion appear until they completely return to normal[39].

Fugl-Meyer assessment

Fugl-Meyer assessment (FMA) is a simplified, time-saving means of evaluating upper- and lower-limb motor function. The index comprises upper-limb (66 points) and lower-limb (34 points) items (total, 100 points). Higher scores reflect better functional recovery. FMA scores can be used to characterize the severity of dyskinesia in stroke patients. Only the lower-limb FMA items will be applied in this study. The passive range of motion of each joint of each participant will be determined before FMA. During the assessment, the non-hemiplegic side will be evaluated first, followed by the hemiplegic side[40].

Timed up-and-go test

The timed up-and-go test is used to assess patients' mobility, balance, walking ability, and fall risk. The participant will sit in a standard armchair with his or her back touching the chair and arms on the armrests. Assistive devices for walking will be placed near the chair. He or she will then be asked to walk to a sign placed at a distance of 3 m at a safe and normal speed, turn around, walk back to the chair, and sit down. The test is complete when the participant's hip touches the seat, and the time taken to complete it (in seconds) will be recorded[41].

Berg balance test

The Berg balance test includes 14 actions, with performance scored on a 0–4 scale (total possible score, 56). Higher scores reflect better balance function. Scores of 0–20 indicate that a patient is safe with wheelchair use, scores of 21–40 indicate that the patient should use an assistive device to walk, and scores of 41–56 indicate that the patient can walk independently; thus, scores < 40 indicate a fall risk[42].

Secondary outcomes

SF-36

It is also called health survey brief table. It comprehensively summarizes the quality of life of the respondents from eight aspects: physiological function, physiological function and mental health. In addition to the above eight aspects, SF-36 also includes another health indicator: HT: reported health transition, which is used to evaluate the overall change of health status in the past year. Evaluation method: the higher the score of each item, the better the health status[39].

MOCA cognitive assessment

The scale will comprehensively evaluate the cognitive function of patients from the aspects of visual space and executive function, naming, memory, attention and language fluency. The full score of the scale is 30 points, ≥ 26 points are normal, 18-26 points are mild cognitive impairment, 10-17 points are moderate cognitive impairment, and less than 10 points are moderate cognitive impairment. If the subject's years of education ≤ 12 years (high school level), the result can be added by 1 point, but the total score cannot exceed 30 points[43].

Patients and public involvement

Participants have not been involved in the study recruitment. The author conceived the initial research questions and outcome measures, and modified according to the telephone interviews with patients and their guardians by a research assistant.In order to assure the safety and feasibility of the intervention, we invited ten stroke patients to learn and practise the whole body vibration training and routine rehabilitation training before designing the RCT. Whole body vibration training and routine rehabilitation training were revised based on the exercise performance and feedback provided by the participants.The burden of the intervention will be assessed by patients and their advisors through face-to-face interviews before signing informed consent.The findings of the study will be disseminated to the participants and their guardians.

Statistical analysis

The statistical analysis will be performed by designated members of the research group who will be blinded to participants' group allocations. All statistical analyses will be conducted using IBM SPSS 24.0. All quantitative data will be summarized and presented using appropriate descriptive statistics, and baseline data from the WBVG，RRTG and CG will be analyzed using the independent-samples *t* test. To explore the effects of the training interventions on stroke patients' motor function and neural plasticity, repeated-measures analysis of variance will be used to examine differences in outcomes between and within groups at all assessment timepoints (Table 6).

Table 6. Overview of the analysis of differences among study groups

	Group	Baseline	12 weeks	4 weeks after intervention	F (P value) Group effect	F (P value) Interaction effect
FMA	WBVT RRT Control					
TUG	WBVT RRT Control					
Berg	WBVT RRT					

	Control					
Brunnstrom	WBVT RRT Control					
Peak torque	WBVT RRT Control					
Mep amplitude	WBVT RRT Control					
SICI	WBVT RRT Control					
M1-pre- SMA	WBVT RRT Control					
MoCA	WBVT RRT Control					
SF-36	WBVT RRT Control					

ETHICS AND DISSEMINATION

All individuals who meet the study criteria will be required to sign an informed consent from prior to enrollment in the study. This study protocol has been approved by the Shanghai University of Sport Research Ethics Committee (102772021RT067). Study findings will be disseminated via publication in peer-reviewed journals and presentations at international conferences.

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Contributorship statement

Mingkai Zhang:Data curation, Writing- Original draft preparation,Writing- Reviewing and Editing.Jianing Wei:Visualization, Investigation.Xueping Wu:Conceptualization, Methodology, SoftwarePriya.

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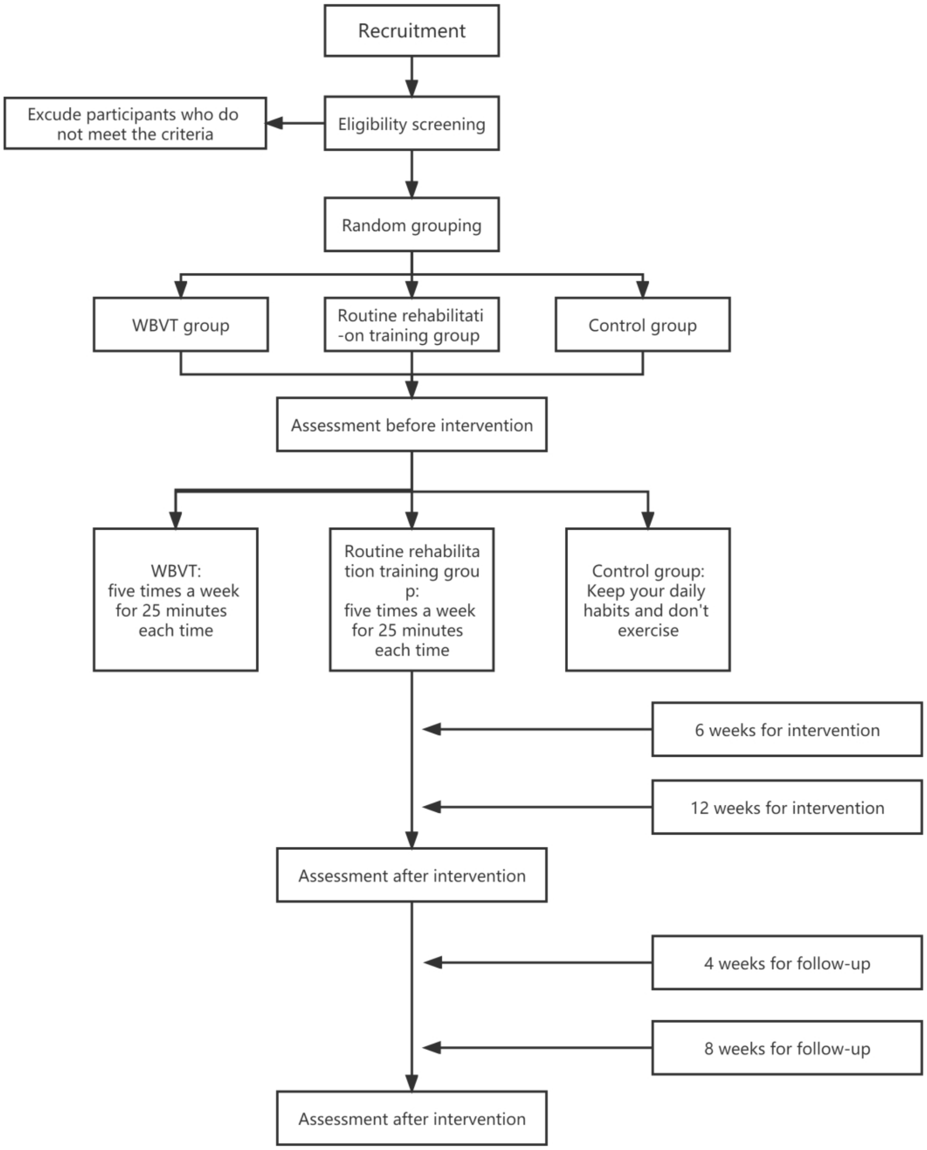
Recruitment
Excude participants who do not meet the criteria
Eligibility screening
Random grouping
WBVT group
Routine rehabilitati -on training group
Control group
Assessment before intervention
WBVT: five times a week for 25 minutes each time
Routine rehabilita tion training grou p: five times a week for 25 minutes each time
Control group: Keep your daily habits and don't exercise
6 weeks for intervention
12 weeks for intervention
Assessment after intervention
4 weeks for follow-up
8 weeks for follow-up
Assessment after intervention

Figure 1

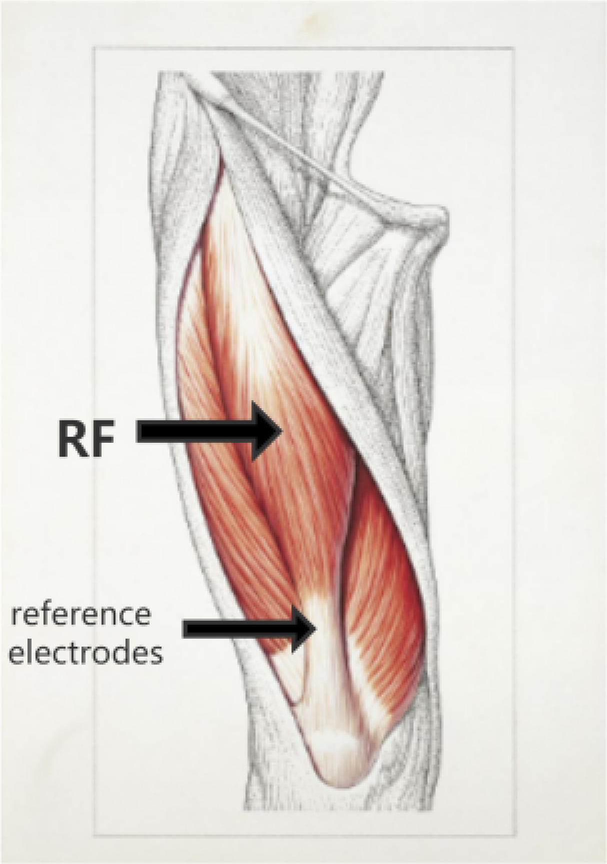

Figure 2 EMG acquisition site

69x86mm (144 x 144 DPI)

Figure Legends

Figure 1 Diagram of study flow

Figure 2 EMG acquisition site

Surface electromyograms will be recorded from the rectus femoris (RF) muscle with 9-mm-diameter Ag-AgCl surface electrodes. The active and reference electrodes will be placed over the rectus femoris abdominis and above the patella, respectively

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Administrative information			
Title	#1	Effects of whole-body vibration training on lower-limb motor function and neural plasticity in stroke patients: protocol for a randomized controlled clinical trial	3
Trial registration	#2a	This study has been registered prospectively in the Chinese Clinical Trail Registry(ChiCTR2200055143)	3
Trial registration: data set	#2b	2022.1-2023.5	
Protocol version	#3	2022.3-2022.10	
Funding	#4	This study was supported by grants from the Research supported by The Program for Overseas High-level talents at Shanghai Institutions of Higher Learning (TP2020063)	16
Roles and	#5a	Mingkai Zhang:Data curation, Writing- Original draft	16

responsibilities: contributorship		preparation,Writing- Reviewing and Editing.	
Roles and responsibilities: sponsor contact information	#5b		
Roles and responsibilities: sponsor and funder	#5c		
Roles and responsibilities: committees	#5d	Jianing Wei:Visualization, Investigation.Xueping Wu:Conceptualization, Methodology, SoftwarePriya.	16
Introduction			
Background and rationale	#6a	Stroke is prevalent and associated with high disability, recurrence, and mortality rates.Stroke patients often have a variety of sequelae. The most common is hemiplegia, which is characterized by numbness and weakness of one limb and continuous increases in muscle tension.The improvement of affected patients' muscle strength, balance, and walking ability is key to the improvement of their lower-limb motor function.Changes in neural plasticity after stroke have been shown to be the basis for the recovery of motor function. Changes in neural plasticity after stroke have been shown to be the basis for the recovery of motor function. In addition to improving muscle strength and joint activity, exercise intervention therapy can aid the recovery of neural plasticity and brain function, thereby promoting the recovery of motor function.The key to effective rehabilitation is to give patients greater motor stimulation within their limited range of activities. As a passive training method, whole-body vibration training (WBVT) involves the generation of mechanical waves through a training platform to stimulate muscle vibration and neuromuscular regulation and adaptation. It has also been found to effectively improve the lower-limb muscle strength, spasm, walking ability, and balance of many people, including stroke patients.	3

Background and rationale: choice of comparators	#6b		
Objectives	#7	We aim to determine the effect of 12 weeks of WBVT on stroke patients' lower-limb motor function and neural plasticity, and explore the difference between wbvt and routine rehabilitation training after 6 and 12 weeks of training. In addition, we will evaluate and compare it after 4 and 8 weeks of stopping training. We will also assess the feasibility of a future full-scale RCT.	6
Trial design	#8	This study was designed as a prospective single-blind RCT. Eligible participants with stroke will be assigned randomly to the whole-body vibration training group (WBVG), routine rehabilitation training group (RRTG), and control group (CG) at a ratio of 1:1:1. The WBVG and RRTG will receive exercise interventions in the Sports Laboratory of Shanghai University of Sport, Shanghai, China. The CG will maintain their routine daily lives. The interventions will be implemented 5 times a week for 12 weeks. Participants will be evaluated at baseline, after 6 and 12 weeks of intervention, and 4 and 8 weeks after intervention termination	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Shanghai university of sport,Shanghai,China	
Eligibility criteria	#10	1)clinical diagnosis of first ischemic or hemorrhagic stroke, 2) Montreal Cognitive Assessment (MoCA) score > 20, 3) Brunnstrom stage III or IV, 4) ability to stand and walk without the help of another person, 5) stable medical condition, and 6) duration of illness ≥ 6 months	7
Interventions: description	#11a	**Table 2.** Vibration training schedule **Table 3.** Routine rehabilitation training **Table 5.** Intervention overview	8

Interventions: modifications	#11b	**Table 5.** Intervention overview	10
Interventions: adherance	#11c	**Table 5.** Intervention overview	10
Interventions: concomitant care	#11d	**Table 5.** Intervention overview	10
Outcomes	#12	**Neural plasticity:**MEP amplitude,Short-interval intracortical inhibition（SICI）,M1–pre-SMA connectivity **Lower-limb motor function:**Peak torque,Brunnstrom stage,Fugl-Meyer assessment,Timed up-and-go test,Berg balance test,36-item Short Form Survey	12
Participant timeline	#13	This study was designed as a prospective single-blind RCT. Eligible participants with stroke will be assigned randomly to the whole-body vibration training group (WBVG), routine rehabilitation training group (RRTG), and control group (CG) at a ratio of 1:1:1. The WBVG and RRTG will receive exercise interventions in the Sports Laboratory of Shanghai University of Sport, Shanghai, China. The CG will maintain their routine daily lives. The interventions will be implemented 5 times a week for	6

		12 weeks. Participants will be evaluated at baseline, after 6 and 12 weeks of intervention, and 4 and 8 weeks after intervention termination	
Sample size	#14	The sample size has been estimated using the G*power statistical software (version 3.1.9.2 for Windows 7 X64; Franz Faul, Kiel University, Germany), used widely for this purpose. In this part of the study, the sample size was estimated by F tests: analysis of variance (ANOVA): related measures, between factors: computer required sample size. Under the significance level of 0.05 and repeated-measures ANOVA setting of 80% efficacy, the total number of subjects needed was determined to be 42 (14 per group). Considering a 20% loss rate, we plan to recruit 60 subjects (20 per group).	8
Recruitment	#15	Participants in Shanghai will be recruited through community outreach, from outpatient clinics, with media advertising, and by telephone. All participants will follow their routine medication and physical therapy/massage regimens during the study period	7
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	This study was designed as a prospective single-blind RCT. Eligible participants with stroke will be assigned randomly to the whole-body vibration training group (WBVG), routine rehabilitation training group (RRTG), and control group (CG) at a ratio of 1:1:1. The WBVG and RRTG will receive exercise interventions in the Sports Laboratory of Shanghai University of Sport, Shanghai, China. The CG will maintain their routine daily lives.Numbers (1–60) will be assigned to the participants according to their recruitment times in an Excel software database, and then a random sequence will be generated using the "= rand ()" formula. This sequence will be sorted to allocate the participants to the study groups.	8
Allocation concealment mechanism	#16b	This study was designed as a prospective single-blind RCT. Eligible participants with stroke will be assigned randomly to the whole-body vibration training group (WBVG), routine rehabilitation training group (RRTG), and control group (CG) at a	8

		ratio of 1:1:1. The WBVG and RRTG will receive exercise interventions in the Sports Laboratory of Shanghai University of Sport, Shanghai, China. The CG will maintain their routine daily lives.Numbers (1–60) will be assigned to the participants according to their recruitment times in an Excel software database, and then a random sequence will be generated using the "= rand ()" formula. This sequence will be sorted to allocate the participants to the study groups.	
Allocation: implementation	#16c		
Blinding (masking)	#17a	The data is analyzed by specialized PhD students, they analyse the data be blind to group allocation.	
Blinding (masking): emergency unblinding	#17b	After the results are processed, the grouping can be announced	
Methods: Data collection, management, and analysis			
Data collection plan	#18a	The data is analyzed by specialized PhD students	
Data collection plan: retention	#18b		
Data management	#19	The data is analyzed by specialized PhD students	
Statistics: outcomes	#20a	The statistical analysis will be performed by designated members of the research group who will be blinded to participants' group allocations. All statistical analyses will be conducted using IBM SPSS 24.0. All quantitative data will be summarized and presented using appropriate descriptive statistics, and baseline data from the WBVG， RRTG and CG will be analyzed using the independent-samples *t* test. To explore the effects of the training interventions on stroke patients' motor function and neural	14

		plasticity, repeated-measures analysis of variance will be used to examine differences in outcomes between and within groups at all assessment timepoints	
Statistics: additional analyses	#20b		
Statistics: analysis population and missing data	#20c		
Methods: Monitoring			
Data monitoring: formal committee	#21a	The data is analyzed by specialized PhD students, they analyse the data be blind to group allocation.	
Data monitoring: interim analysis	#21b		
Harms	#22	In the Participants gave an informed consent form	
Auditing	#23	In the Participants gave an informed consent form	
Ethics and dissemination			
Research ethics approval	#24	This study has been approved by the Shanghai University of Sport Research Ethics Committee (102772021RT067)	3
Protocol amendments	#25	Upload as attachment	
Consent or assent	#26a	PhD students in charge of data collection will collect data within the TMS and lower limbs function will be conducted before the intervention as well as at 6 weeks, 12 weeks, and 4 weeks and 8weeks after the intervention	
Consent or assent:	#26b		

ancillary studies		
Confidentiality	#27	Professor Wu, who is in charge of recruitment, completes the participant information management.
Declaration of interests	#28	The authors have no conflicts of interest to declare
Data access	#29	The result will be made public by the person in charge of the Research supported by The Program for Overseas High-level talents at Shanghai Institutions of Higher Learning (TP2020063)
Ancillary and post trial care	#30	In the Participants gave an informed consent form.
Dissemination policy: trial results	#31a	This study has been registered prospectively in the Chinese Clinical Trail Registry(ChiCTR2200055143,1 January 2022).It will be published in accordance with the standards of the Chinese Clinical Trial Registry
Dissemination policy: authorship	#31b	It will be written in accordance with the standards of the Chinese Clinical Trial Registry.
Dissemination policy: reproducible research	#31c	It can be viewed in the Chinese Clinical Trial Registry.
Appendices		
Informed consent materials	#32	Upload as attachment.
Biological specimens	#33	None

Effects of whole-body vibration training on lower-limb motor function and neural plasticity in stroke patients: protocol for a randomized controlled clinical trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-060796.R1
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Complete List of Authors:	Zhang, Mingkai; Shanghai University of Sport jianing, wei; Shanghai University of Sport, School of Psychology Wu, Xueping; Shanghai University of Sport
Primary Subject Heading:	Sports and exercise medicine
Secondary Subject Heading:	Sports and exercise medicine
Keywords:	Stroke < NEUROLOGY, SPORTS MEDICINE, REHABILITATION MEDICINE

Title: Effects of whole-body vibration training on lower-limb motor function and neural plasticity in stroke patients: protocol for a randomized controlled clinical trial

Article Type: Clinical Study Protocol

Keywords: Stroke; Whole-body vibration training; Lower-limbs; Neural plasticity;

Study protocol

Author:

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Corresponding Author's Institution: Shanghai University of Sport

ABSTRACT

Introduction Lower-limb motor dysfunction is very common in stroke patients, and usually caused by brain neural connectivity disorder. Studies have shown that whole-body vibration training (WBVT) significantly improves lower-limb motor function in stroke patients, and may promote nerve remodeling. The prior purpose of this study is to explore the effects of WBVT on lower-limb motor function and neuroplasticity in stroke patients. Therefore exloring the feasibility of formal experiments.

Methods A single-blind randomized controlled trial will be conducted. Sixty stroke patients will be recruited and allocated randomly to WBVT, routine rehabilitation training (RRT), and control group (CG). The WBVT and RRT interventions will be implemented as five 25-min sessions weekly for continuous 12 weeks; the CG will remain daily habitual living styles and routine treatments, in community or hospital, and will also receive telephone follow-up and health-related lectures. Transcranial magnetic stimulation will be used to assess neural plasticity while lower-limb motor function is assessed using indicators of strength, walking ability, and joint activity. The assessments will be conducted at the period of baseline, Week 6, Week 12, as well as upon 4 and 8 weeks respectively after intervention completion.

Ethics and dissemination This study has been approved by the Shanghai University of Sport Research Ethics Committee (102772021RT067) and will provide data on the effects of WBVT relative to RRT in terms of the improvement of stroke patients' lower-limb motor function and neural plasticity. The results of this study can provide a theoretical basis for the application of WBVT for stroke patients. The results of this study will be disseminated via publications in peer-reviewed journals and presentations at international conference.

Trail registration number： This study has been registered prospectively in the Chinese Clinical Trail Registry(ChiCTR2200055143,1 January 2022).

Type of Manuscript: Clinical Study Protocol

Figures and tables: 2 figures and 6 tables

Number of Words: Abstract: 286 words; Manuscript: 4,570 words

Abbreviations

WBVT, Whole-body vibration training

RRT, routine rehabilitation training

MEP,Motor evoked potential

Pre-SMA,pre-supplementary motor area

FMA,Fugl-Meyer assessment

TUG,Time up and go

Effects of whole-body vibration training on lower-limb motor function and neural plasticity in stroke patients: protocol for a randomized controlled clinical trial

ABSTRACT

Introduction Lower-limb motor dysfunction is common in stroke patients, and usually caused by brain neural connectivity disorder. Previous studies have shown that the whole-body vibration training (WBVT) significantly improves the lower-limb motor function in stroke patients, and may promote nerve remodeling. The prior purpose of this study is to explore the effects of WBVT on lower-limb motor function and neuroplasticity in stroke patients. Therefore exloring the feasibility of formal experiments.

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Strengths and limitations of this study

1. This protocol present a rigorous design of a randomized controlled trial that aims to explore the effects of WBVT on lower-limb motor function and neuroplasticity in patients who had a stroke.
2. An accurate measurement tool and multiple indicators will be used to judge the effects of WBVT on neuroplasticity in patients who had a stroke.
3. If the result we will reach is positive,then that will provide a powerful evidence of WBVT on improve lower-limb motor function and neuroplasticity in stroke survivors.
4. The patients will come from one geographic area which limits the generalisability.

INTRODUCTION

Stroke is prevalent and associated with high disability, recurrence, and mortality rates.[1] The latest global burden of disease study demonstrates that the overall lifetime risk of stroke in China is 39.9%, ranking the first in the world, stroke is also the leading cause among diseases of lost years of life in China.[2] Stroke patients often have a variety of sequelae. The most common is hemiplegia, which is characterized by numbness, weakness of one limb and spasticity. It significantly reduces patients' abilities to perform daily activities and impacts their quality of life.[3] Lower-limb motor function can be restored to a limited extent in more than 70% of hemiplegic patients, and most of such cannot obtain a good gait or walking speed.[4] Lower-limb motor dysfunction after stroke is caused by central nervous system injuries resulting in abnormal movement patterns.[5] Its main characteristics are poor muscle strength,[6] spasticity,[5] joint instability,[7] associated reactions,[8] and synergy movement.[9] Thus, the improvement of affected patients' muscle strength, balance ability, and walking ability is critical in restoring their lower-limb motor function.

Neural plasticity generally refers to the nervous system's inherent abilitties to make structural and functional changes to adapt to changes in the internal and external environments.[10] Changes in neural plasticity after stroke have been shown to be the foundation of the recovery of motor function.[11] After unilateral stroke, the neural plasticity includes two aspects: a) changes in neural synaptic connections and b) changes in the excitability of various structures. Functional recovery after stroke is related to changes in the motor cortex and other regions regarding the brain's anatomical structure and function.[12] The presence of lesions on one side of the cerebral hemisphere reduces or inhibits the excitability of the motor cortex on that side, while the cortex of the contralateral hemisphere will be hyperexcitable.[13] Therefore, maladaptive neural plasticity exists, which regard to the hindered functional recovery of the development of an unwanted symptom , such as compensatory movement pattern, delayed-onset involuntary abnormal movement.[14] The primary motor cortex (M1) provides the main outputs to the descending motor system and autonomous motor commands. Such mechanism is closely linked to somatosensory and spatial processing in the parietal lobe, premotor cortex, and supplementary motor area; therefore, changes in M1's excitability will affect motor function.[15] M1 is also defined as the scalp site where the minimum stimulation intensity causes the maximum motor evoked potential (MEP) of the muscle. Thus, changes in the MEP reflect the conditions of motor function.[16] The pre-supplementary motor area (pre-SMA), located in between the prefrontal lobe and motor system, is responsible for functions such as language and idea generation, action recognition, working memory maintenance, learning, and the execution of action sequences.[17] The enhancement of pre-SMA activity has been found to alleviate M1 disorders in stroke patients, and changes in connectivity between motor areas may contribute to the improvements of the patients' motor function.[18] Therefore, the recovery of lower-limb motor function in stroke patients correlates to the functional connectivity between cerebral hemispheres, as well as the normalization of the bilateral sensorimotor cortical network.

Exercise intervention therapy has the advantages of compliance, minimal side effects, and strong operability. It has become an important means of rehabilitation for stroke patients[19]. Functional recovery after stroke is a complex process. The repeated sensory input is among the most effective means of improving the cortical structure and body function [20]. In addition, early intervention, task-oriented training, and repetitive intensity are also determinants of motor function recovery after stroke.[21] The repeated performance of specific actions during exercise has been found to construct motor memory, which is a form of brain plasticity improvement[22]. In addition to improving muscle strength and joint activity, exercise intervention therapy can aid the improvement of neural plasticity and brain function, thereby promoting the recovery of motor function.[23] However, patients' defected motor function and executive function will potentially make it difficult for them to effectively remember and perform complex rehabilitation. In that way, the effectiveness of rehabilitation is compromised.[24] Thus, the key to an effective rehabilitation is to enable patients to exercise as much as possible only if within their limited range of physical activity.

Whole-body vibration training (WBVT) is an exercise or treatment method used in sport, physiotherapy and rehabilitation.[25][26] During WBVT, people sit, stand, or exercise on a vibrating platform that generate vibration.[27] WBVT was found to activate the muscle spindles, thereby inducing reflex muscle activation.[28] It has also been found to effectively improve the lower-limb muscle strength,[29] spasticity,[30] walking ability,[31] and balance[32] of many people, including stroke patients.[33] In addition, a review of the clinical application of WBVT in patients with chronic stroke showed that its main effects include promotion of muscle contraction, stimulation of the proprioceptive system, and improvement of motor control ability .[34] WBVT has also been shown to increase oxygen consumption and promote the release of vasodilators in stroke patients, without additional effects on the heart rates or blood pressure.[35] Thus, a period of WBVT can improve blood perfusion on the affected side in stroke patients.[36] In addition, a transcranial magnetic stimulation (TMS) study revealed significant changes in cortical excitability after vibration training in healthy people[37]. The convergence of evidence from several experimental studies suggests that WBVT induces the reorganization of sensory motor processes in healthy people’s brain.[29] It may also promote functional recovery after stroke by enhancing the proprioceptive afferents of the central nervous system.[24] Emperical evidence suggested that after a period of WBVT, TMS study found three dominant changes on the sample stroke patients: their motor thresholds decreased; their MEP amplitudes increased; and their flexor muscle activation improved.[32] The scholars concluded that changes in cortical excitability were related to motor function, and that WBVT was a suitable non-drug treatment to promote the recovery of neural plasticity and motor function in stroke patients, even if the patients were in the chronic phase.[32] Thus, WBVT can effectively improve the motor function of stroke patients, and may also have a strong effect on brain neural plasticity. However, limited research on this topic has been conducted, and scholars have reached different conclusions. In addition, the type and parameter of effective WBVT has not been explicitly identified; further research is needed.

In sum, little research has examined the application of WBVT for the rehabilitation of stroke patients, and especially the positive and negative impacts of WBVT on these patients' brain function. Thus, this randomized controlled trial (RCT) was designed to examine the impacts of WBVT on stroke patients’ lower-limb motor function and neural plasticity. Lower-limb motor function will be evaluated by isokinetic muscle strength and other assessment method, and TMS will be used to examine changes in neural plasticity.

AIMS AND OBJECTIVES

This study aim to determine the effect of 12 weeks of WBVT on stroke patients’ lower-limb motor function and neural plasticity, and explore the difference between wbvt and routine rehabilitation training after 6 and 12 weeks of training. In addition, this study will evaluate and compare it after 4 and 8 weeks of stopping training. The feasibility of a future full-scale RCT will be assessed.

The study objectives are to:

a).clarify the effects of WBVT on stroke patients’ lower-limb motor function and neural plasticity;

b).analyze the training effects and maintenance times of the two training methods;

c).explore the facilitators, barriers, and contextual factors influencing the implementation of WBVT;

d).test the acceptability of the data collection procedures used.

METHODS AND DESIGN

Study design

This study was designed as a prospective single-blind RCT. Eligible participants with stroke will be assigned randomly to the whole-body vibration training group (WBVG), routine rehabilitation training group (RRTG), and control group (CG) at a ratio of 1:1:1. The CG will maintain daily living and routine treatment, in community or hospital, and will also receive telephone follow-up and lectures. On this basis, the WBVG and RRTG will receive exercise interventions in the Sports Laboratory of Shanghai University of Sport, Shanghai, China. The interventions will be implemented 5 times a week for 12 weeks and 25min a day. The training will be arranged from Monday to Friday.Participants will be evaluated at baseline, after 6 and 12 weeks of intervention, and 4 and 8 weeks after intervention termination (Figure 1). This research protocol has been approved by the research ethics committee of Shanghai University of Sport (no. 102772021RT067).The study is scheduled to begin in September 2022 and continue until January 2023.

Figure 1. Diagram of study flow.

Participants

Participants in Shanghai will be recruited through community outreach, from outpatient clinics, with media advertising, and by telephone. All participants will follow their routine medication and physical therapy/massage regimens during the study period. They will provide written informed consent before inclusion in the study. Before and after the intervention, data on participants' demographic and clinical characteristics will be collected and analyzed (Table 1).

Table 1. Demographic and clinical characteristics of participants

	WBVG	RRTG	CG
Age			
Gender			
BMI			
Time of illness			
Stroke type			
Affected side			
Whether auxiliary equipment is used			
FMA score			
Berg score			
TUG			
MoCA score			
SF-36			

Note：WBVG，Whole-body vibration training group；RRTG，routine rehabilitation training group；CG，control group;BMI,body mass index;FMA,Fugl-Meyer assessment;TUG,Time up and go;MoCA,Montreal Cognitive Assessment;SF-36,the MOS item short from health survey

Inclusion and exclusion criteria

The inclusion criteria will be: a) The included cases met the inclusion criteria of stroke in the classification scheme of various cerebrovascular diseases formulated by the Fourth National Academic Conference on cerebrovascular diseases in 1995, and were confirmed by cranial CT or MRI, b) Brunnstrom stage IV, c) ability to stand and walk without the help of another person, d) stable medical condition, e) aged 50-75 years, f) duration of illness ≥ 3 months, g）no serious organ disease, h) no vibration training experience. The exclusion criteria will be: a) It does not meet the diagnostic criteria of stroke in the classification scheme of various cerebrovascular diseases formulated by the fourth national cerebrovascular disease academic conference in 1995, and there is no head CT or MRI confirmation; b) other nervous system disease, c) severe skeletal muscle or cardiovascular disease, d) severe lumbar disc herniation, e) dysfunction or failure of the heart, lung, liver, kidney, or other major organ, f) other serious disease or exercise contraindication, and g) vibration training experience.

Sample size

The sample size has been estimated using the G*power statistical software (version 3.1.9.2 for Windows 7 X64; Franz Faul, Kiel University, Germany), used widely for this purpose. In this part of the study, the sample size was estimated by F tests: analysis of variance (ANOVA): related measures, between factors: computer required sample size. Under the significance level of 0.05 and repeated-measures ANOVA setting of 80% efficacy, the total number of subjects needed was determined to be 42 (14 per group). Considering a 20% loss rate, we plan to recruit 60 subjects (20 per group).

Randomization

Eligible participants will be randomised into Whole-body vibration training group, routine rehabilitation training group and control group at 1:1:1 ratio after consenting and baseline assessment.Excel software will be used to code the subjects in 1-60 according to the recruitment time,and then use the formula "= RAND ()" to generated the corresponding random sequence. By sorting the random sequence and then grouping it, 60 subjects will be randomly grouped. These tasks will be completed by professional computer workers blinded to recruitment and allocation after the completion of recruitment.

Interventions

WBVT intervention

Because of the stroke characteristics, patients usually have weak muscle strength in the lower limbs and poor balance, they will better accept low-frequency vibration training[38], which has been shown to be more likely to induce changes in brain nerve excitation[**Error! Bookmark not defined.**]. The WBVT intervention will be implemented using a vibrating platform (I-vib5050A; Bodygreen, Taiwan) that generates vertical vibrations and has an adjustable frequency range (6–12 Hz) . During WBVT sessions, the subjects will wear shoes to stand on a vibrating paltform. The vibration frequency will be increased in a stepwise manner in three phases (weeks 1–4, 5–8, and 9–12) over the 12-week intervention period. The training will consist of adaptation to the vibration (6, 7, and 7 Hz, respectively, in phases 1–3) with 5 minutes of static standing, 1 minute of rest, two rounds of 5 minutes of rhythmic half-squat to standing practice (alternation of 60° knee flexion and standing for 5 seconds each) with vertical vibration (8, 10, and 12 Hz, respectively, in phases 1–3) and 1 minute rest between rounds, 5 minutes of vertical vibration (8, 10, and 12 Hz, respectively, in phases 1–3) under traction created by the placement of a ~4-cm-thick towel under the front sole of the foot to bend the patient's ankle back and pull the calf muscles with 1 minute rest between rounds, and a final 5 minutes of standing with vibration (6, 7, and 7 Hz, respectively, in phases 1–3). The peak-to-peak displacement will be maintained at 4 mm in all phases. The participants will be monitored continuously during training, and training will be terminated immediately upon complaint of any abnormal condition, such as panic, chest tightness, dizziness, or pain (Table 2).

Table 2. Whole-body vibration training schedule

Time	Vibration time（min）	Schedule（min）	Vibration frequency（Hz）
Phase I			
Week 1 and 2	25	5-5-5-5-5	6-8
Week 3 and 4	25	5-5-5-5-5	6-8
Phase II			
Week 5 and 6	25	5-5-5-5-5	7-10
Week 7 and 8	25	5-5-5-5-5	7-10
Phase III			
Week 9 and 10	25	5-5-5-5-5	7-12
Week 11 and 12	25	5-5-5-5-5	7-12

Routine rehabilitation exercise intervention

The routine rehabilitation exercise intervention will consist of in-situ alternate leg lifting with the feet at shoulder width (while in a safe, stable position and with the help of both hands/arms), in-situ squatting (to 60–90°, increasingly gradually according to the patient’s condition) with the feet at shoulder width (while holding a protective rod), in-situ heel lifting while on a step with the feet at shoulder width (while holding a protective rod), and walking on a treadmill equipped with safety handrails (Table 3). Their exercise intensity will be monitored using the Borg scale (Table 4)[39].

Control group

These participants will be requested to maintain their original habits of lifestyle.They will receive usual care including usual stroke services available to the participants, including but not limited to, medical consultations offered by hospital, rehabilitation services by community-based organisations.

Participants in the control group will receive telephone follow-up and health lectures but will not receive any specific exercise training from the study scheme.

The specific intervention details of the three groups are shown in Table 5.[40]

Table 3. Routine rehabilitation training

Phase	Exercise	Repetitions/duration
I: weeks 1–4		
	Alternating in-situ leg lifts	2 rounds of 30 s, inter-round interval to complete recovery
	In-situ squats	2 rounds of 8–10 repetitions, inter-round interval to complete recovery
	Step heel lifts	2 rounds of 15 repetitions, inter-round interval to complete recovery

	Walking	5 min
II: weeks 5–8		
	Alternating in-situ leg lifts	3 rounds of 30 s, inter-round intervals to complete recovery
	In-situ squats	3 rounds of 8–10 repetitions, inter-round intervals to complete recovery
	Step heel lifts	3 rounds of 15 repetitions, inter-round intervals to complete recovery
	Walking	10 min
III: weeks 9–12		
	Alternating in-situ leg lifts	3 rounds of 30 s, inter-round intervals to complete recovery
	In-situ squats	4 rounds of 8–10 repetitions, inter-round intervals to complete recovery
	Step heel lifts	4 rounds of 15 repetitions, inter-round intervals to complete recovery
	Walking	10 minutes

Table 4. Borg scale

Level	Description
6	No exertion at all
7	Extremely light
8	Light
9	Very light (easy, slow walking at a comfortable pace)
10	This is the effort level where you can't hear your breath
11	You are able to easily talk and you can run at this level for a long time
12	Light (you are building aerobic endurance)
13	Somewhat hard (you are making quite an effort; you feel tired but can continue)
14	You start to hear your breath, but are not gasping for air
15	You can talk, but it is more challenging, you use one- or two-word answers
16	Hard (this is considered to be your steady state)
17	Very hard (very strenuous and you are very fatigued)
18	Your breathing is vigorous, you can't talk, you are gasping for air
19	Extremely hard (you are counting the minutes until it ends)
20	Maximal exertion

Table 5. [40] Exercise intervention TIDieR

Item no.	Brief name	Group WBVG	 RRTG	 CG
1	Why	WBVT	Routine rehabilitation training	Control
2	What	12 weeks training under the guidance of professionals		Maintenance of usual living habits, no exercise advice, regular attendance of health lectures, telephone follow-up
3	What (content)	25 min exercise, five times/week		Attendance of fortnightly health lectures, monthly telephone interviews
4	What (procedure)	Evaluation at baseline ,6 weeks and 12 weeks, and 4 and 8 weeks after intervention termination,reporting of results to participants so that they can understand the physical changes occurring		
5	Who (administrators)	WBVT coach is a professional rehabilitation physician, assessments performed by Shanghai University of Sport PhD students	Routine rehabilitation training coach is a professional rehabilitation physician, assessments performed by Shanghai University of Sport PhD students	Health lectures and telephone interviews performed by Shanghai University of Sport PhD students (College of Physical Education and Training)
6	How	The exercise interventions will take place in a stationary gymnasium, the instructors will direct the whole group face to face		The health lectures will be held in the conference room of the College of Physical Education and Training, Shanghai University of Sport
7	When and how much	See Table 2	See Table 3	Health lectures, 30–50 min; interviews, 10 min
8	How well	Participants will receive regular feedback, including physical and psychological data and reports on their motor skills learning performance; they will be kept up to date on their progress and status to keep them engaged		

Note:TIDieR, Template for intervention Description and Replication;[40] WBVG, whole-body vibration training group; RRTG, routine rehabilitation training group; CG,control group;WBVT, whole-body vibration training.

Transcranial magnetic stimulation (TMS) protocol

Electromyographic recording

Surface electromyograms will be recorded from the rectus femoris (RF) muscle with 9-mm-diameter Ag-AgCl surface electrodes. The electrode will be placed on the muscle belly of the RF, and the reference electrode will be located above the patella. (Figure 2). The signal will be amplified (1000×), bandpass filtered (2–2.5 kHz; Intronix Technologies Model), digitized at 5 kHz by an analog–digital interface (Micro1401; Cambridge Electronics Design, Cambridge, UK), and saved for offline analysis.

TMS

TMS will be applied to the bilateral M1 with a figure-of-eight–shaped coil (7-cm external loop diameter) connected to two single-pulse monophasic stimulators (Magstim Co., Whitland, Dyfeld, UK). The M1 hotspot will be defined as the scalp location inducing the largest peak–peak MEP amplitude in the contralateral RF muscle. The handle of the test stimulus (TS) coil will be angled posteriorly 30–45° from the midsagittal line. TS1mV will be defined as the lowest TMS intensity required to generate MEPs of 1 mV in the relaxed RF muscle in at least 5 of 10 trials. The resting motor threshold (RMT) will be defined as the lowest TMS intensity required to generate MEPs > 50 V in at least 5 of 10 trials with the target muscle completely relaxed[41].

Figure 2. EMG acquisition site.

Isokinetic strength assessment protocol

Due to the particularities of the participants' conditions, for safety reasons and based on previous isokinetic muscle strength research, the angular velocity for isokinetic strength testing in both lower limbs will 60°/s. The testing instrument will be warmed up and debugged before assessment. The assessment will be performed after an adaptability exercise with the participant's body fixed and his or her hands placed in front of the chest. The test action will be repeated five times with intervening 90-s rest intervals. The average peak torque of the flexor and extensor muscles of the knee joint will be taken as the measure of strength. The peak torque is the gold-standard measure for isokinetic assessment, and has shown high degrees of accuracy and repeatability[42].

Outcomes

Primary outcome

Neural plasticity

MEP amplitude

MEPs will be recorded during TMS. MEP amplitudes will be measured as peak-to-peak values.

Short-interval intracortical inhibition（SICI）

The intensity of the conditioning stimulus(CS) is 80%RMT or 90%RMT ,the intensity of test stimulus（TS） is 1MV. The interstimulus intervals (ISIs) will be 2, 3, and 4 ms. Each block will contain 40 trials in random order[43][44].

M1–pre-SMA connectivity

To investigate changes in connectivity between the left M1 and pre-SMA after long-term exercise training, the two high-power Magstim 200 devices and two figure-of-eight coil sites will be performed with TMS. Coil placement will be performed as in a similar hemispheric study to avoid overlap[45]. The smaller CS coil will be placed over the right hemisphere to induce a medially directed current in the brain, and will be used to stimulate the pre-SMA. The TS coil will be placed over the leg representation of the left hemisphere for the induction of a posterior–anterior current in the brain. The CS will be delivered by an octagonal coil (50-mm diameter) to stimulate the pre-SMA. Its intensity will be 110% or 90% of the RMT. The angle between the placement direction and the scalp midline will be 45° to induce a front-to-back current[46]. The TS (M1) intensity will be set to evoke a resting MEP with the same TMS coil. The ISIs will be 6, 8, 10, 30, 40, and 50 ms. The strength of the CS will be changed for each block, and complete the order pseudo-random for each subject block. Each block will contain 60 trials. Separate TS will be collected 10 times. The MEP of each ISI will be collected 10 times, for a total of 70 measurements. Each block will contain 70 trials in random order.

Lower-limb motor function

Peak torque

Participants' lower-limb flexion and extension muscle strength will be measured by using the Biodex isokinetic testing system (Biodex Medical System 4, NY, USA) [47] at all assessment timepoints.

Brunnstrom stage

The Brunnstrom approach is a set of treatment methods for dyskinesia after central nervous system injury developed by Swedish physiotherapist Signe Brunnstrom. Motor function recovery is divided into six stages, with muscle tension increasing gradually from low to high and joint reaction, joint movement, and spasm gradually becoming significant. With the completion of common motion, separation motion, and fine motion appear until they completely return to normal[48].

Fugl-Meyer assessment

Fugl-Meyer assessment (FMA) is a simplified, time-saving means of evaluating upper- and lower-limb motor function. The index comprises upper-limb (66 points) and lower-limb (34 points) items (total, 100 points). Higher scores reflect better functional recovery. FMA scores can be used to characterize the severity of dyskinesia in stroke patients. Only the lower-limb FMA items will be applied in this study. The passive range of motion of each joint of each participant will be determined before FMA. During the assessment, the non-hemiplegic side will be evaluated first, followed by the hemiplegic side[49].

Timed up-and-go test

The timed up-and-go test is used to assess patients' mobility, balance, walking ability, and fall risk. The participant will sit in a standard armchair with his or her back touching the chair and arms on the armrests. Assistive devices for walking will be placed near the chair. He or she will then be asked to walk to a sign placed at a distance of 3 m at a safe and normal speed, turn around, walk back to the chair, and sit down. The test is complete when the participant's hip touches the seat, and the time taken to complete it (in seconds) will be recorded[50].

Berg balance test

The Berg balance test includes 14 actions, with performance scored on a 0–4 scale (total possible score, 56). Higher scores reflect better balance function. Scores of 0–20 indicate that a patient is safe with wheelchair use, scores of 21–40 indicate that the patient should use an assistive device to walk, and scores of 41–56 indicate that the patient can walk independently; thus, scores < 40 indicate a fall risk[51].

Secondary outcomes

the MOS item short from health survey(SF-36)

It is also called health survey brief table. It comprehensively summarizes the quality of life of the respondents from eight aspects: physiological function, physiological function and mental health. In addition to the above eight aspects, SF-36 also includes another health indicator: HT: reported health transition, which is used to evaluate the overall change of health status in the past year. Evaluation method: the higher the score of each item, the better the health status[48].

Montreal Cognitive Assessment(MOCA)

The scale will comprehensively evaluate the cognitive function of patients from the aspects of visual space and executive function, naming, memory, attention and language fluency. The full score of the scale is 30 points, ≥ 26 points are normal, 18-26 points are mild cognitive impairment, 10-17 points are moderate cognitive impairment, and less than 10 points are moderate cognitive impairment. If the subject's years of education ≤ 12 years (high school level), the result can be added by 1 point, but the total score cannot exceed 30 points[52].

Patients and public involvement

Participants have not been involved in the study recruitment. The author conceived the initial research questions and outcome measures, and modified according to the telephone interviews with patients and their guardians by a research assistant.In order to assure the safety and feasibility of the intervention, ten stroke patients will be invited to learn and practise the whole-body vibration training and routine rehabilitation training before designing the RCT. Whole-body vibration training and routine rehabilitation training were revised based on the exercise performance and feedback provided by the participants.The burden of the intervention will be assessed by patients and their advisors through face-to-face interviews before signing informed consent.The findings of the study will be disseminated to the participants and their guardians.

Statistical analysis

The statistical analysis will be performed by designated members of the research group who will be blinded to participants' group allocations. All statistical analyses will be conducted using IBM SPSS 24.0. All quantitative data will be summarized and presented using appropriate descriptive statistics, and baseline data from the WBVG ， RRTG and CG will be analyzed using the independent-samples *t* test. To explore the effects of the training interventions on stroke patients' motor function and neural plasticity, repeated-measures analysis of variance will be used to examine differences in outcomes between and within groups at all assessment timepoints (Table 6).

Table 6. Overview of the analysis of differences among study groups

	Group	Baseline	12 weeks	4 weeks after intervention	F (P value) Group effect	F (P value) Interaction effect
FMA	WBVT RRT Control					
TUG	WBVT RRT Control					
Berg	WBVT RRT Control					
Brunnstrom	WBVT RRT Control					
Peak torque	WBVT RRT Control					
Mep amplitude	WBVT RRT Control					
SICI	WBVT RRT Control					
M1-pre- SMA	WBVT RRT Control					

MoCA	WBVT RRT Control					
SF-36	WBVT RRT Control					

Note: WBVT,whole-body vibration training; RRT,routine rehabilitation training; FMA,Fugl-Meyer assessment;TUG,Time up and go;MoCA,Montreal Cognitive Assessment;SF-36,the MOS item short from health survey;SICI,Short-interval intracortical inhibition;M1, primary motor cortex;pre-SMA,pre-supplementary motor area

ETHICS AND DISSEMINATION

All individuals who meet the study criteria will be required to sign an informed consent from prior to enrollment in the study. This study protocol has been approved by the Shanghai University of Sport Research Ethics Committee (102772021RT067). Study findings will be disseminated via publication in peer-reviewed journals and presentations at international conferences.

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Contributorship statement

Mingkai Zhang: Data curation, Writing- Original draft preparation,Writing- Reviewing and Editing. Jianing Wei: Visualization, Investigation. Xueping Wu: Conceptualization, Methodology, SoftwarePriya.

Competing interests

There are no competing interests for any authors.

Figure legends

Figure 1. Diagram of study flow.

Note:WBVT,Whole-body vibration training

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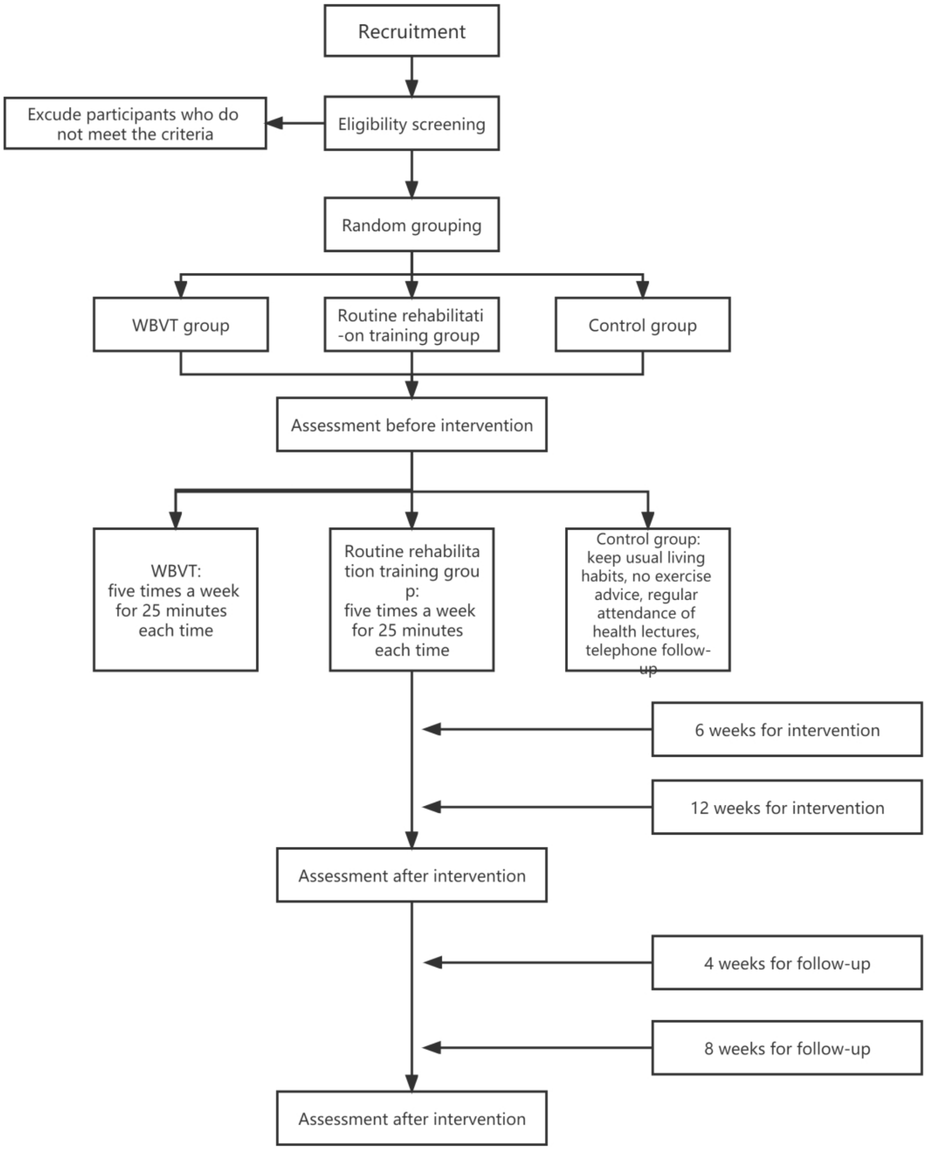

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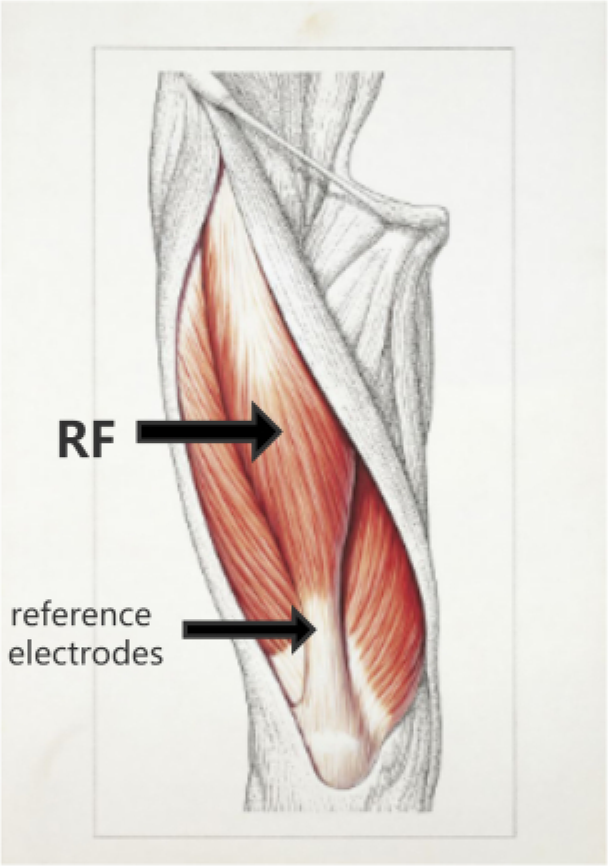

Figure 2 EMG acquisition site

69x86mm (144 x 144 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Effects of whole-body vibration training on lower-limb motor function and neural plasticity in stroke patients: protocol for a randomized controlled clinical trial	3
Trial registration	#2a	This study has been registered prospectively in the Chinese Clinical Trail Registry(ChiCTR2200055143)	3
Trial registration: data set	#2b	2022.1-2023.5	
Protocol version	#3	2022.3-2022.10	
Funding	#4	This study was supported by grants from the Research supported by The Program for Overseas High-level talents at Shanghai Institutions of Higher Learning (TP2020063)	16
Roles and	#5a	Mingkai Zhang:Data curation, Writing- Original draft	16

responsibilities: contributorship		preparation,Writing- Reviewing and Editing.	
Roles and responsibilities: sponsor contact information	#5b		
Roles and responsibilities: sponsor and funder	#5c		
Roles and responsibilities: committees	#5d	Jianing Wei:Visualization, Investigation.Xueping Wu:Conceptualization, Methodology, SoftwarePriya.	16
Introduction			
Background and rationale	#6a	Stroke is prevalent and associated with high disability, recurrence, and mortality rates.Stroke patients often have a variety of sequelae. The most common is hemiplegia, which is characterized by numbness and weakness of one limb and continuous increases in muscle tension.The improvement of affected patients' muscle strength, balance, and walking ability is key to the improvement of their lower-limb motor function.Changes in neural plasticity after stroke have been shown to be the basis for the recovery of motor function. Changes in neural plasticity after stroke have been shown to be the basis for the recovery of motor function. In addition to improving muscle strength and joint activity, exercise intervention therapy can aid the recovery of neural plasticity and brain function, thereby promoting the recovery of motor function.The key to effective rehabilitation is to give patients greater motor stimulation within their limited range of activities. As a passive training method, whole-body vibration training (WBVT) involves the generation of mechanical waves through a training platform to stimulate muscle vibration and neuromuscular regulation and adaptation. It has also been found to effectively improve the lower-limb muscle strength, spasm, walking ability, and balance of many people, including stroke patients.	3

Background and rationale: choice of comparators	#6b		
Objectives	#7	We aim to determine the effect of 12 weeks of WBVT on stroke patients' lower-limb motor function and neural plasticity, and explore the difference between wbvt and routine rehabilitation training after 6 and 12 weeks of training. In addition, we will evaluate and compare it after 4 and 8 weeks of stopping training. We will also assess the feasibility of a future full-scale RCT.	6
Trial design	#8	This study was designed as a prospective single-blind RCT. Eligible participants with stroke will be assigned randomly to the whole-body vibration training group (WBVG), routine rehabilitation training group (RRTG), and control group (CG) at a ratio of 1:1:1. The WBVG and RRTG will receive exercise interventions in the Sports Laboratory of Shanghai University of Sport, Shanghai, China. The CG will maintain their routine daily lives. The interventions will be implemented 5 times a week for 12 weeks. Participants will be evaluated at baseline, after 6 and 12 weeks of intervention, and 4 and 8 weeks after intervention termination	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Shanghai university of sport,Shanghai,China	
Eligibility criteria	#10	1)clinical diagnosis of first ischemic or hemorrhagic stroke, 2) Montreal Cognitive Assessment (MoCA) score > 20, 3) Brunnstrom stage III or IV, 4) ability to stand and walk without the help of another person, 5) stable medical condition, and 6) duration of illness ≥ 6 months	7
Interventions: description	#11a	**Table 2.** Vibration training schedule **Table 3.** Routine rehabilitation training **Table 5.** Intervention overview	8

Interventions: modifications	#11b	**Table 5.** Intervention overview	10
Interventions: adherance	#11c	**Table 5.** Intervention overview	10
Interventions: concomitant care	#11d	**Table 5.** Intervention overview	10
Outcomes	#12	**Neural plasticity:**MEP amplitude,Short-interval intracortical inhibition（SICI）,M1–pre-SMA connectivity **Lower-limb motor function:**Peak torque,Brunnstrom stage,Fugl-Meyer assessment,Timed up-and-go test,Berg balance test,36-item Short Form Survey	12
Participant timeline	#13	This study was designed as a prospective single-blind RCT. Eligible participants with stroke will be assigned randomly to the whole-body vibration training group (WBVG), routine rehabilitation training group (RRTG), and control group (CG) at a ratio of 1:1:1. The WBVG and RRTG will receive exercise interventions in the Sports Laboratory of Shanghai University of Sport, Shanghai, China. The CG will maintain their routine daily lives. The interventions will be implemented 5 times a week for	6

		12 weeks. Participants will be evaluated at baseline, after 6 and 12 weeks of intervention, and 4 and 8 weeks after intervention termination	
Sample size	#14	The sample size has been estimated using the G*power statistical software (version 3.1.9.2 for Windows 7 X64; Franz Faul, Kiel University, Germany), used widely for this purpose. In this part of the study, the sample size was estimated by F tests: analysis of variance (ANOVA): related measures, between factors: computer required sample size. Under the significance level of 0.05 and repeated-measures ANOVA setting of 80% efficacy, the total number of subjects needed was determined to be 42 (14 per group). Considering a 20% loss rate, we plan to recruit 60 subjects (20 per group).	8
Recruitment	#15	Participants in Shanghai will be recruited through community outreach, from outpatient clinics, with media advertising, and by telephone. All participants will follow their routine medication and physical therapy/massage regimens during the study period	7
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	This study was designed as a prospective single-blind RCT. Eligible participants with stroke will be assigned randomly to the whole-body vibration training group (WBVG), routine rehabilitation training group (RRTG), and control group (CG) at a ratio of 1:1:1. The WBVG and RRTG will receive exercise interventions in the Sports Laboratory of Shanghai University of Sport, Shanghai, China. The CG will maintain their routine daily lives.Numbers (1–60) will be assigned to the participants according to their recruitment times in an Excel software database, and then a random sequence will be generated using the "= rand ()" formula. This sequence will be sorted to allocate the participants to the study groups.	8
Allocation concealment mechanism	#16b	This study was designed as a prospective single-blind RCT. Eligible participants with stroke will be assigned randomly to the whole-body vibration training group (WBVG), routine rehabilitation training group (RRTG), and control group (CG) at a	8

		ratio of 1:1:1. The WBVG and RRTG will receive exercise interventions in the Sports Laboratory of Shanghai University of Sport, Shanghai, China. The CG will maintain their routine daily lives.Numbers (1–60) will be assigned to the participants according to their recruitment times in an Excel software database, and then a random sequence will be generated using the "= rand ()" formula. This sequence will be sorted to allocate the participants to the study groups.	
Allocation: implementation	#16c		
Blinding (masking)	#17a	The data is analyzed by specialized PhD students, they analyse the data be blind to group allocation.	
Blinding (masking): emergency unblinding	#17b	After the results are processed, the grouping can be announced	
Methods: Data collection, management, and analysis			
Data collection plan	#18a	The data is analyzed by specialized PhD students	
Data collection plan: retention	#18b		
Data management	#19	The data is analyzed by specialized PhD students	
Statistics: outcomes	#20a	The statistical analysis will be performed by designated members of the research group who will be blinded to participants' group allocations. All statistical analyses will be conducted using IBM SPSS 24.0. All quantitative data will be summarized and presented using appropriate descriptive statistics, and baseline data from the WBVG， RRTG and CG will be analyzed using the independent-samples *t* test. To explore the effects of the training interventions on stroke patients' motor function and neural	14

		plasticity, repeated-measures analysis of variance will be used to examine differences in outcomes between and within groups at all assessment timepoints	
Statistics: additional analyses	#20b		
Statistics: analysis population and missing data	#20c		
Methods: Monitoring			
Data monitoring: formal committee	#21a	The data is analyzed by specialized PhD students, they analyse the data be blind to group allocation.	
Data monitoring: interim analysis	#21b		
Harms	#22	In the Participants gave an informed consent form	
Auditing	#23	In the Participants gave an informed consent form	
Ethics and dissemination			
Research ethics approval	#24	This study has been approved by the Shanghai University of Sport Research Ethics Committee (102772021RT067)	3
Protocol amendments	#25	Upload as attachment	
Consent or assent	#26a	PhD students in charge of data collection will collect data within the TMS and lower limbs function will be conducted before the intervention as well as at 6 weeks, 12 weeks, and 4 weeks and 8weeks after the intervention	
Consent or assent:	#26b		

ancillary studies		
Confidentiality	#27	Professor Wu, who is in charge of recruitment, completes the participant information management.
Declaration of interests	#28	The authors have no conflicts of interest to declare
Data access	#29	The result will be made public by the person in charge of the Research supported by The Program for Overseas High-level talents at Shanghai Institutions of Higher Learning (TP2020063)
Ancillary and post trial care	#30	In the Participants gave an informed consent form.
Dissemination policy: trial results	#31a	This study has been registered prospectively in the Chinese Clinical Trail Registry(ChiCTR2200055143,1 January 2022).It will be published in accordance with the standards of the Chinese Clinical Trial Registry
Dissemination policy: authorship	#31b	It will be written in accordance with the standards of the Chinese Clinical Trial Registry.
Dissemination policy: reproducible research	#31c	It can be viewed in the Chinese Clinical Trial Registry.
Appendices		
Informed consent materials	#32	Upload as attachment.
Biological specimens	#33	None

BMJ Open

Effects of whole-body vibration training on lower-limb motor function and neural plasticity in stroke patients: protocol for a randomized controlled clinical trial

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Study protocol

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Abbreviations

WBVT, Whole-body vibration training

RRT, routine rehabilitation training

MEP,Motor evoked potential

Pre-SMA,pre-supplementary motor area

FMA,Fugl-Meyer assessment

TUG,Timed up and go

Effects of whole-body vibration training on lower-limb motor function and neural plasticity in stroke patients: protocol for a randomized controlled clinical trial

ABSTRACT

Introduction Lower-limb motor dysfunction is common in stroke patients, and usually caused by brain neural connectivity disorder. Previous studies have shown that the whole-body vibration training (WBVT) significantly improves the lower-limb motor function in stroke patients, and may promote nerve remodeling. The prior purpose of this study is to explore effects of WBVT on lower-limb motor function and neuroplasticity in stroke patients.

Methods A single-blind randomized controlled trial will be conducted. Sixty stroke patients will be recruited and allocated randomly to WBVT, routine rehabilitation training (RRT), and control group (CG). The WBVT and RRT interventions will be implemented as five 25-min sessions weekly for continuous 12 weeks; the CG will remain daily habitual living styles and routine treatments, in community or hospital, and will also receive telephone follow-up and health-related lectures. Transcranial magnetic stimulation will be used to assess neural plasticity while lower-limb motor function is assessed using indicators of strength, walking ability, and joint activity. The assessments will be conducted at the period of baseline, Week 6, Week 12, as well as upon 4 and 8 weeks respectively after intervention completion.

Ethics and dissemination This study has been approved by the Shanghai University of Sport Research Ethics Committee (102772021RT067) and will provide data on the effects of WBVT relative to RRT in terms of the improvement of stroke patients' lower-limb motor function and neural plasticity. The results of this study will be disseminated via publications in peer-reviewed journals and presentations at international conference.

Trail registration number： This study has been registered prospectively in the Chinese Clinical Trail Registry(ChiCTR2200055143,1 January 2022).

Strengths and limitations of this study

1. This protocol presents a rigorous design of a randomized controlled trial that aims to explore the effects of WBVT on lower-limb motor function and neuroplasticity in patients who had a stroke.
2. An accurate measurement tool and multiple indicators will be used to judge the effects of WBVT on neuroplasticity in patients who had a stroke.
3. The patients will come from one geographic area which limits the generalisability.

INTRODUCTION

Stroke is prevalent and associated with high disability, recurrence, and mortality rates.[1] The latest global burden of disease study demonstrates that the overall lifetime risk of stroke in China is 39.9%, ranking the first in the world, stroke is also the leading cause among diseases of lost years of life in China.[2] Stroke patients often have a variety of sequelae. The most common is hemiplegia, which is characterized by numbness, weakness of one limb and spasticity. It significantly reduces patients' abilities to perform daily activities and impacts their quality of life.[3] Lower-limb motor function can be restored to a limited extent in more than 70% of hemiplegic patients, and most of such cannot obtain a good gait or walking speed.[4] Lower-limb motor dysfunction after stroke is caused by central nervous system injuries resulting in abnormal movement patterns.[5] Its main characteristics are poor muscle strength,[6] spasticity,[5] joint instability,[7] associated reactions,[8] and synergy movement.[9] Thus, the improvement of affected patients' muscle strength, balance ability, and walking ability is critical in restoring their lower-limb motor function.

Neural plasticity generally refers to the nervous system's inherent abilitties to make structural and functional changes to adapt to changes in the internal and external environments.[10] Changes in neural plasticity after stroke have been shown to be the foundation of the recovery of motor function.[11] After unilateral stroke, the neural plasticity includes two aspects: a) changes in neural synaptic connections and b) changes in the excitability of various structures. Functional recovery after stroke is related to changes in the motor cortex and other regions regarding the brain's anatomical structure and function.[12] The presence of lesions on one side of the cerebral hemisphere reduces or inhibits the excitability of the motor cortex on that side, while the cortex of the contralateral hemisphere will be hyperexcitable.[13] Therefore, maladaptive neural plasticity exists, which regard to the hindered functional recovery of the development of an unwanted symptom , such as compensatory movement pattern, delayed-onset involuntary abnormal movement.[14] The primary motor cortex (M1) provides the main outputs to the descending motor system and autonomous motor commands. Such mechanism is closely linked to somatosensory and spatial processing in the parietal lobe, premotor cortex, and supplementary motor area; therefore, changes in M1's excitability will affect motor function.[15] M1 is also defined as the scalp site where the minimum stimulation intensity causes the maximum motor evoked potential (MEP) of the muscle. Thus, changes in the MEP reflect the conditions of motor function.[16] The pre-supplementary motor area (pre-SMA), located in between the prefrontal lobe and motor system, is responsible for functions such as language and idea generation, action recognition, working memory maintenance, learning, and the execution of action sequences.[17] The enhancement of pre-SMA activity has been found to alleviate M1 disorders in stroke patients, and changes in connectivity between motor areas may contribute to the improvements of the patients' motor function.[18] Therefore, the recovery of lower-limb motor function in stroke patients correlates to the functional connectivity between cerebral hemispheres, as well as the normalization of the bilateral sensorimotor cortical network.

Exercise intervention therapy has the advantages of compliance, minimal side effects, and strong operability. It has become an important means of rehabilitation for stroke patients[19]. Functional recovery after stroke is a complex process. The repeated sensory input is among the most effective means of improving the cortical structure and body function [20]. In addition, early intervention, task-oriented training, and repetitive intensity are also determinants of motor function recovery after stroke.[21] The repeated performance of specific actions during exercise has been found to construct motor memory, which is a form of brain plasticity improvement[22]. In addition to improving muscle strength and joint activity, exercise intervention therapy can aid the improvement of neural plasticity and brain function, thereby promoting the recovery of motor function.[23] However, patients' defected motor function and executive function will potentially make it difficult for them to effectively remember and perform complex rehabilitation. In that way, the effectiveness of rehabilitation is compromised.[24] Thus, the key to an effective rehabilitation is to enable patients to exercise as much as possible only if within their limited range of physical activity.

Whole-body vibration training (WBVT) is an exercise or treatment method used in sport, physiotherapy and rehabilitation.[25][26] During WBVT, people sit, stand, or exercise on a vibrating platform that generate vibration.[27] WBVT was found to activate the muscle spindles, thereby inducing reflex muscle activation.[28] It has also been found to effectively improve the lower-limb muscle strength,[29] spasticity,[30] walking ability,[31] and balance[32] of many people, including stroke patients.[33] In addition, a review of the clinical application of WBVT in patients with chronic stroke showed that its main effects include promotion of muscle contraction, stimulation of the proprioceptive system, and improvement of motor control ability .[34] WBVT has also been shown to increase oxygen consumption and promote the release of vasodilators in stroke patients, without additional effects on the heart rates or blood pressure.[35] Thus, a period of WBVT can improve blood perfusion on the affected side in stroke patients.[36] In addition, a transcranial magnetic stimulation (TMS) study revealed significant changes in cortical excitability after vibration training in healthy people[37]. The convergence of evidence from several experimental studies suggests that WBVT induces the reorganization of sensory motor processes in healthy people's brain.[29] It may also promote functional recovery after stroke by enhancing the proprioceptive afferents of the central nervous system.[24] A previous TMS study demonstrated that after a period of WBVT, stroke patients have lower motor thresholds and higher MEP amplitudes, along with improved activation of flexors.[32] The study concluded that WBVT is a suitable nonpharmacological therapy to promote the recovery of neural plasticity and motor function in stroke patients, even if the patients were in the chronic phase.[32] Thus, WBVT can effectively improve the motor function of stroke patients, and may also have a strong effect on brain neural plasticity. However, limited research on this topic has been conducted, and scholars have reached different conclusions. In addition, the type and parameter of effective WBVT has not been explicitly identified; further research is needed.

In sum, little research has examined the application of WBVT for the rehabilitation of stroke patients, and especially the positive and negative impacts of WBVT on these patients' brain function. Thus, this randomized controlled trial (RCT) was designed to examine the impacts of WBVT on stroke patients’ lower-limb motor function and neural plasticity. Lower-limb motor function will be evaluated by isokinetic muscle strength and other assessment method, and TMS will be used to examine changes in neural plasticity.

AIMS AND OBJECTIVES

This study aims to determine the effect of 12 weeks of WBVT on stroke patients’ lower-limb motor function and neural plasticity, and explore the difference between wbvt and routine rehabilitation training after 6 and 12 weeks of training. In addition, this study will evaluate and compare it after 4 and 8 weeks of stopping training. The feasibility of a future full-scale RCT will be assessed.

The study objectives are to:

a).clarify the effects of WBVT on stroke patients’ lower-limb motor function and neural plasticity;

b).analyze the training effects and maintenance times of the two training methods;

c).explore the facilitators, barriers, and contextual factors influencing the implementation of WBVT;

d).test the acceptability of the data collection procedures used.

METHODS AND DESIGN

Study design

This study was designed as a prospective single-blind RCT. Eligible participants with stroke will be assigned randomly to the whole-body vibration training group (WBVG), routine rehabilitation training group (RRTG), and control group (CG) at a ratio of 1:1:1. The CG will maintain daily living and routine treatment, in community or hospital, and will also receive telephone follow-up and lectures. On this basis, the WBVG and RRTG will receive exercise interventions in the Sports Laboratory of Shanghai University of Sport, Shanghai, China. The interventions will be implemented 5 times a week for 12 weeks and 25min a day. The training will be arranged from Monday to Friday.Participants will be evaluated at baseline, after 6 and 12 weeks of intervention, and 4 and 8 weeks after intervention termination (Figure 1). This research protocol has been approved by the research ethics committee of Shanghai University of Sport (no. 102772021RT067).The study is scheduled to begin in September 2022 and continue until January 2023.

Figure 1. Diagram of study flow.

Participants

Participants in Shanghai will be recruited through community outreach, from outpatient clinics, with media advertising, and by telephone. All participants will follow their routine medication and physical therapy/massage regimens during the study period. They will provide written informed consent before inclusion in the study. Before and after the intervention, data on participants' demographic and clinical characteristics will be collected and analyzed (Table 1).

Table 1. Demographic and clinical characteristics of participants

	WBVG	RRTG	CG
Age			
Gender			
BMI			
Time of illness			
Stroke type			
Affected side			
Whether auxiliary equipment is used			
FMA score			
Berg score			
TUG			
MoCA score			
SF-36			

Note： WBVG， Whole-body vibration training group； RRTG， routine rehabilitation training group；CG，control group;BMI,body mass index;FMA,Fugl-Meyer assessment;TUG,Timed up and go;MoCA,Montreal Cognitive Assessment;SF-36,the MOS item short from health survey

Inclusion and exclusion criteria

The inclusion criteria will be: a) The included cases met the inclusion criteria of stroke in the classification scheme of various cerebrovascular diseases formulated by the Fourth National Academic Conference on cerebrovascular diseases in 1995, and were confirmed by cranial CT or MRI, b) Brunnstrom stage IV, c) ability to stand and walk without the help of another person, d) stable medical condition, e) aged 50-75 years, f) duration of illness ≥ 3 months, g） no serious organ disease, h) no vibration training experience. The exclusion criteria will be: a) It does not meet the diagnostic criteria of stroke in the classification scheme of various cerebrovascular diseases formulated by the fourth national cerebrovascular disease academic conference in 1995, and there is no head CT or MRI confirmation; b) other nervous system disease, c) severe skeletal muscle or cardiovascular disease, d) severe lumbar disc herniation, e) dysfunction or failure of the heart, lung, liver, kidney, or other major organ, f) other serious disease or exercise contraindication, and g) vibration training experience.

Sample size

The sample size has been estimated using the G*power statistical software (version 3.1.9.2 for Windows 7 X64; Franz Faul, Kiel University, Germany), used widely for this purpose. In this part of the study, the sample size was estimated by F tests: analysis of variance (ANOVA): related measures, between factors: computer required sample size. Under the significance level of 0.05 and repeated-measures ANOVA setting of 80% efficacy, the total number of subjects needed was determined to be 42 (14 per group). Considering a 20% loss rate, we plan to recruit 60 subjects (20 per group).

Randomization

Eligible participants will be randomised into Whole-body vibration training group, routine rehabilitation training group and control group at 1:1:1 ratio after consenting and baseline assessment.Excel software will be used to code the subjects in 1-60 according to the recruitment time,and then use the formula "= RAND ()" to generated the corresponding random sequence. By sorting the random sequence and then grouping it, 60 subjects will be randomly grouped. These tasks will be completed by professional computer workers blinded to recruitment and allocation after the completion of recruitment.

Interventions

WBVT intervention

Because of the stroke characteristics, patients usually have weak muscle strength in the lower limbs and poor balance, they will better accept low-frequency vibration training[38], which has been shown to be more likely to induce changes in brain nerve excitation[**Error! Bookmark not defined.**]. The WBVT intervention will be implemented using a vibrating platform (I-vib5050A; Bodygreen, Taiwan) that generates vertical vibrations and has an adjustable frequency range (6–12 Hz) . During WBVT sessions, the subjects will wear shoes to stand on a vibrating paltform. The vibration frequency will be increased in a stepwise manner in three phases (weeks 1–4, 5–8, and 9–12) over the 12-week intervention period. The training will consist of adaptation to the vibration (6, 7, and 7 Hz, respectively, in phases 1–3) with 5 minutes of static standing, 1 minute of rest, two rounds of 5 minutes of rhythmic half-squat to standing practice (alternation of 60° knee flexion and standing for 5 seconds each) with vertical vibration (8, 10, and 12 Hz, respectively, in phases 1–3) and 1 minute rest between rounds, 5 minutes of vertical vibration (8, 10, and 12 Hz, respectively, in phases 1–3) under traction created by the placement of a ~4-cm-thick towel under the front sole of the foot to bend the patient's ankle back and pull the calf muscles with 1 minute rest between rounds, and a final 5 minutes of standing with vibration (6, 7, and 7 Hz, respectively, in phases 1–3). The peak-to-peak displacement will be maintained at 4 mm in all phases. The participants will be monitored continuously during training, and training will be terminated immediately upon complaint of any abnormal condition, such as panic, chest tightness, dizziness, or pain (Table 2).

Table 2. Whole-body vibration training schedule

Time	Vibration time（min）	Schedule（min）	Vibration frequency（Hz）

Phase I			
Week 1 and 2	25	5-5-5-5-5	6-8
Week 3 and 4	25	5-5-5-5-5	6-8
Phase II			
Week 5 and 6	25	5-5-5-5-5	7-10
Week 7 and 8	25	5-5-5-5-5	7-10
Phase III			
Week 9 and 10	25	5-5-5-5-5	7-12
Week 11 and 12	25	5-5-5-5-5	7-12

Routine rehabilitation exercise intervention

The routine rehabilitation exercise intervention will consist of in-situ alternate leg lifting with the feet at shoulder width (while in a safe, stable position and with the help of both hands/arms), in-situ squatting (to 60–90°, increasingly gradually according to the patient's condition) with the feet at shoulder width (while holding a protective rod), in-situ heel lifting while on a step with the feet at shoulder width (while holding a protective rod), and walking on a treadmill equipped with safety handrails (Table 3). Their exercise intensity will be monitored using the Borg scale (Table 4)[39].

Control group

These participants will be requested to maintain their original habits of lifestyle.They will receive usual care including usual stroke services available to the participants, including but not limited to, medical consultations offered by hospital, rehabilitation services by community-based organisations.

Participants in the control group will receive telephone follow-up and health lectures but will not receive any specific exercise training from the study scheme.

The specific intervention details of the three groups are shown in Table 5.[40]

Table 3. Routine rehabilitation training

Phase	Exercise	Repetitions/duration
I: weeks 1–4		
	Alternating in-situ leg lifts	2 rounds of 30 s, inter-round interval to complete recovery
	In-situ squats	2 rounds of 8–10 repetitions, inter-round interval to complete recovery
	Step heel lifts	2 rounds of 15 repetitions, inter-round interval to complete recovery
	Walking	5 min
II: weeks 5–8		

	Alternating in-situ leg lifts	3 rounds of 30 s, inter-round intervals to complete recovery
	In-situ squats	3 rounds of 8–10 repetitions, inter-round intervals to complete recovery
	Step heel lifts	3 rounds of 15 repetitions, inter-round intervals to complete recovery
	Walking	10 min
III: weeks 9–12		
	Alternating in-situ leg lifts	3 rounds of 30 s, inter-round intervals to complete recovery
	In-situ squats	4 rounds of 8–10 repetitions, inter-round intervals to complete recovery
	Step heel lifts	4 rounds of 15 repetitions, inter-round intervals to complete recovery
	Walking	10 minutes

Table 4. Borg scale

Level	Description
6	No exertion at all
7	Extremely light
8	Light
9	Very light (easy, slow walking at a comfortable pace)
10	This is the effort level where you can't hear your breath
11	You are able to easily talk and you can run at this level for a long time
12	Light (you are building aerobic endurance)
13	Somewhat hard (you are making quite an effort; you feel tired but can continue)
14	You start to hear your breath, but are not gasping for air
15	You can talk, but it is more challenging, you use one- or two-word answers
16	Hard (this is considered to be your steady state)
17	Very hard (very strenuous and you are very fatigued)
18	Your breathing is vigorous, you can't talk, you are gasping for air
19	Extremely hard (you are counting the minutes until it ends)
20	Maximal exertion

Table 5. [40] Exercise intervention TIDieR

		Group		
Item no.	Brief name	WBVG	RRTG	CG
1	Why	WBVT	Routine rehabilitation training	Control
2	What	12 weeks training under the guidance of professionals		Maintenance of usual living habits, no exercise advice, regular attendance of health lectures, telephone follow-up
3	What (content)	25 min exercise, five times/week		Attendance of fortnightly health lectures, monthly telephone interviews
4	What (procedure)	Evaluation at baseline ,6 weeks and 12 weeks, and 4 and 8 weeks after intervention termination,reporting of results to participants so that they can understand the physical changes occurring		
5	Who (administrators)	WBVT coach is a professional rehabilitation physician, assessments performed by Shanghai University of Sport PhD students	Routine rehabilitation training coach is a professional rehabilitation physician, assessments performed by Shanghai University of Sport PhD students	Health lectures and telephone interviews performed by Shanghai University of Sport PhD students (College of Physical Education and Training)
6	How	The exercise interventions will take place in a stationary gymnasium, the instructors will direct the whole group face to face		The health lectures will be held in the conference room of the College of Physical Education and Training, Shanghai University of Sport
7	When and how much	See Table 2	See Table 3	Health lectures, 30–50 min; interviews, 10 min
8	How well	Participants will receive regular feedback, including physical and psychological data and reports on their motor skills learning performance; they will be kept up to date on their progress and status to keep them engaged		

Note:TIDieR, Template for intervention Description and Replication;[40] WBVG, whole-body vibration training group; RRTG, routine rehabilitation training group; CG,control group;WBVT, whole-body vibration training.

Transcranial magnetic stimulation (TMS) protocol

Electromyographic recording

Surface electromyograms will be recorded from the rectus femoris (RF) muscle with 9-mm-diameter Ag-AgCl surface electrodes. The electrode will be placed on the muscle belly of the RF, and the reference electrode will be located above the patella. (Figure 2). The signal will be amplified (1000×), bandpass filtered (2–2.5 kHz; Intronix

Technologies Model), digitized at 5 kHz by an analog–digital interface (Micro1401; Cambridge Electronics Design, Cambridge, UK), and saved for offline analysis.

TMS

TMS will be applied to the bilateral M1 with a figure-of-eight–shaped coil (7-cm external loop diameter) connected to two single-pulse monophasic stimulators (Magstim Co., Whitland, Dyfeld, UK). The M1 hotspot will be defined as the scalp location inducing the largest peak–peak MEP amplitude in the contralateral RF muscle. The handle of the test stimulus (TS) coil will be angled posteriorly 30–45° from the midsagittal line. TS1mV will be defined as the lowest TMS intensity required to generate MEPs of 1 mV in the relaxed RF muscle in at least 5 of 10 trials. The resting motor threshold (RMT) will be defined as the lowest TMS intensity required to generate MEPs > 50 V in at least 5 of 10 trials with the target muscle completely relaxed[41].

Figure 2. EMG acquisition site.

Isokinetic strength assessment protocol

Due to the particularities of the participants' conditions, for safety reasons and based on previous isokinetic muscle strength research, the angular velocity for isokinetic strength testing in both lower limbs will 60°/s. The testing instrument will be warmed up and debugged before assessment. The assessment will be performed after an adaptability exercise with the participant's body fixed and his or her hands placed in front of the chest. The test action will be repeated five times with intervening 90-s rest intervals. The average peak torque of the flexor and extensor muscles of the knee joint will be taken as the measure of strength. The peak torque is the gold-standard measure for isokinetic assessment, and has shown high degrees of accuracy and repeatability[42].

Outcomes

Primary outcome

Neural plasticity

MEP amplitude

MEPs will be recorded during TMS. MEP amplitudes will be measured as peak-to-peak values.

Short-interval intracortical inhibition（SICI）

The intensity of the conditioning stimulus(CS) is 80%RMT or 90%RMT ,the intensity of test stimulus（TS） is 1MV. The interstimulus intervals (ISIs) will be 2, 3, and 4 ms. Each block will contain 40 trials in random order[43][44].

M1–pre-SMA connectivity

To investigate changes in connectivity between the left M1 and pre-SMA after long-term exercise training, the two high-power Magstim 200 devices and two figure-of-eight coil sites will be performed with TMS. Coil placement will be performed as in a similar hemispheric study to avoid overlap[45]. The smaller CS coil will be placed over the right hemisphere to induce a medially directed current in the brain, and will be used to stimulate the pre-SMA. The TS coil will be placed over the leg representation of the left hemisphere for the induction of a posterior–anterior current in the brain. The CS will be delivered by an octagonal coil (50-mm diameter) to stimulate the pre-SMA. Its intensity will be 110% or 90% of the RMT. The angle between the placement direction and the scalp midline will be 45° to induce a front-to-back current[46]. The TS (M1) intensity will be set to evoke a resting MEP with the same TMS coil. The ISIs will be 6, 8, 10, 30, 40, and 50 ms. The strength of the CS will be changed for each block, and complete the order pseudo-random for each subject block. Each block will contain 60 trials. Separate TS will be collected 10 times. The MEP of each ISI will be collected 10 times, for a total of 70 measurements. Each block will contain 70 trials in random order.

Lower-limb motor function

Peak torque

Participants' lower-limb flexion and extension muscle strength will be measured by using the Biodex isokinetic testing system (Biodex Medical System 4, NY, USA) [47] at all assessment timepoints.

Brunnstrom stage

The Brunnstrom approach is a set of treatment methods for dyskinesia after central nervous system injury developed by Swedish physiotherapist Signe Brunnstrom. Motor function recovery is divided into six stages, with muscle tension increasing gradually from low to high and joint reaction, joint movement, and spasm gradually becoming significant. With the completion of common motion, separation motion, and fine motion appear until they completely return to normal[48].

Fugl-Meyer assessment

Fugl-Meyer assessment (FMA) is a simplified, time-saving means of evaluating upper- and lower-limb motor function. The index comprises upper-limb (66 points) and lower-limb (34 points) items (total, 100 points). Higher scores reflect better functional recovery. FMA scores can be used to characterize the severity of dyskinesia in stroke patients. Only the lower-limb FMA items will be applied in this study. The passive range of motion of each joint of each participant will be determined before FMA. During the assessment, the non-hemiplegic side will be evaluated first, followed by the hemiplegic side[49].

Timed up-and-go test

The timed up-and-go test is used to assess patients' mobility, balance, walking ability, and fall risk. The participant will sit in a standard armchair with his or her back touching the chair and arms on the armrests. Assistive devices for walking will be placed near the chair. He or she will then be asked to walk to a sign placed at a distance of 3 m at a safe and normal speed, turn around, walk back to the chair, and sit down. The test is complete when the participant's hip touches the seat, and the time taken to complete it (in seconds) will be recorded[50].

Berg balance test

The Berg balance test includes 14 actions, with performance scored on a 0–4 scale (total possible score, 56). Higher scores reflect better balance function. Scores of 0–20 indicate that a patient is safe with wheelchair use, scores of 21–40 indicate that the patient should use an assistive device to walk, and scores of 41–56 indicate that the patient can walk independently; thus, scores < 40 indicate a fall risk[51].

Patients and public involvement

Participants have not been involved in the study recruitment. The author conceived the initial research questions and outcome measures, and modified according to the telephone interviews with patients and their guardians by a research assistant.In order to assure the safety and feasibility of the intervention, ten stroke patients will be invited to learn and practise the whole-body vibration training and routine rehabilitation training before designing the RCT. Whole-body vibration training and routine rehabilitation training were revised based on the exercise performance and feedback provided by the participants.The burden of the intervention will be assessed by patients and their advisors through face-to-face interviews before signing informed consent.The findings of the study will be disseminated to the participants and their guardians.

Statistical analysis

The statistical analysis will be performed by designated members of the research group who will be blinded to participants' group allocations. All statistical analyses will be conducted using IBM SPSS 24.0. All quantitative data will be summarized and presented using appropriate descriptive statistics, and baseline data from the WBVG，RRTG and CG will be analyzed using the independent-samples *t* test. To explore the effects of the training interventions on stroke patients' motor function and neural plasticity, repeated-measures analysis of variance will be used to examine differences in outcomes between and within groups at all assessment timepoints (Table 6).

Table 6. Overview of the analysis of differences among study groups

	Group	Baseline	12 weeks	4 weeks after intervention	F (P value) Group effect	F (P value) Interaction effect
FMA	WBVT RRT Control					
TUG	WBVT					

	RRT Control					
Berg	WBVT RRT Control					
Brunnstrom	WBVT RRT Control					
Peak torque	WBVT RRT Control					
Mep amplitude	WBVT RRT Control					
SICI	WBVT RRT Control					
M1-pre- SMA	WBVT RRT Control					
MoCA	WBVT RRT Control					
SF-36	WBVT RRT Control					

Note: WBVT,whole-body vibration training; RRT,routine rehabilitation training; FMA,Fugl-Meyer assessment;TUG,Time up and go;MoCA,Montreal Cognitive Assessment;SF-36,the MOS item short from health survey;SICI,Short-interval intracortical inhibition;M1, primary motor cortex;pre-SMA,pre-supplementary motor area

ETHICS AND DISSEMINATION

All individuals who meet the study criteria will be required to sign an informed consent from prior to enrollment in the study. This study protocol has been approved by the Shanghai University of Sport Research Ethics Committee (102772021RT067). Study findings will be disseminated via publication in peer-reviewed journals and presentations at international conferences.

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Contributorship statement

Mingkai Zhang: Data curation, Writing- Original draft preparation,Writing- Reviewing

and Editing. Jianing Wei: Visualization, Investigation. Xueping Wu: Conceptualization, Methodology, SoftwarePriya.

Competing interests

There are no competing interests for any authors.

Figure legends

Figure 1. Diagram of study flow.

Note:WBVT,Whole-body vibration training

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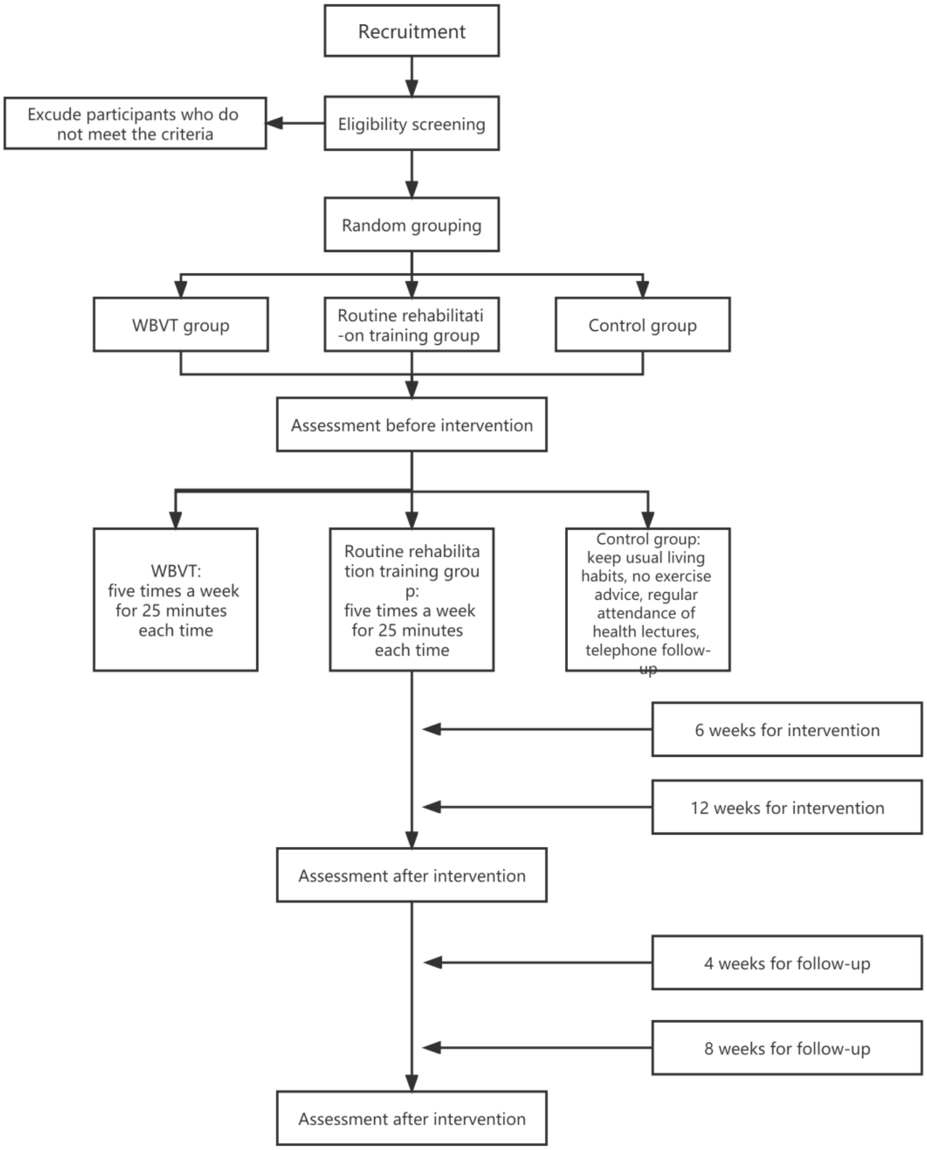
ability, VO2peak and cost of walking in stroke survivors: preliminary results of a pilot randomized controlled trial." *Eur J Phys Rehabil Med* 54.3 (2018): 408-418.doi:10.23736/S1973-9087.16.04224-6

[dataset] [51] Gordon, C. D. , R. Wilks , and A. Mccaw-Binns . Data from: "Effect of aerobic exercise (walking) training on functional status and health-related quality of life in chronic stroke survivors: a randomized controlled trial. " *Stroke* 44.4(2013):1179-1181.doi: 10.1161/STROKEAHA.111.000642



840x1029mm (72 x 72 DPI)

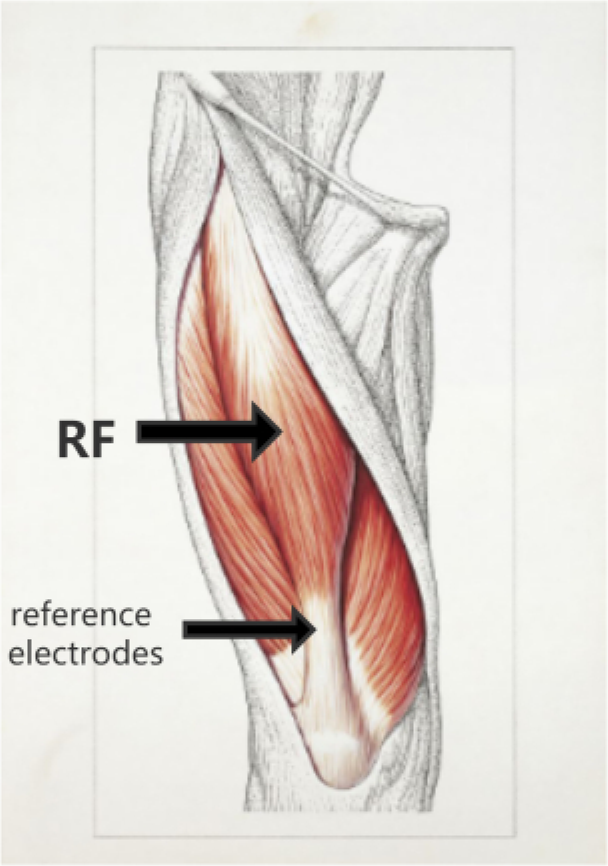


Figure 2 EMG acquisition site

69x86mm (144 x 144 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Effects of whole-body vibration training on lower-limb motor function and neural plasticity in stroke patients: protocol for a randomized controlled clinical trial	3
Trial registration	#2a	This study has been registered prospectively in the Chinese Clinical Trail Registry(ChiCTR2200055143)	3
Trial registration: data set	#2b	2022.1-2023.5	
Protocol version	#3	2022.3-2022.10	
Funding	#4	This study was supported by grants from the Research supported by The Program for Overseas High-level talents at Shanghai Institutions of Higher Learning (TP2020063)	16
Roles and	#5a	Mingkai Zhang:Data curation, Writing- Original draft	16

responsibilities: contributorship		preparation,Writing- Reviewing and Editing.	
Roles and responsibilities: sponsor contact information	#5b		
Roles and responsibilities: sponsor and funder	#5c		
Roles and responsibilities: committees	#5d	Jianing Wei:Visualization, Investigation.Xueping Wu:Conceptualization, Methodology, SoftwarePriya.	16
Introduction			
Background and rationale	#6a	Stroke is prevalent and associated with high disability, recurrence, and mortality rates.Stroke patients often have a variety of sequelae. The most common is hemiplegia, which is characterized by numbness and weakness of one limb and continuous increases in muscle tension.The improvement of affected patients' muscle strength, balance, and walking ability is key to the improvement of their lower-limb motor function.Changes in neural plasticity after stroke have been shown to be the basis for the recovery of motor function. Changes in neural plasticity after stroke have been shown to be the basis for the recovery of motor function. In addition to improving muscle strength and joint activity, exercise intervention therapy can aid the recovery of neural plasticity and brain function, thereby promoting the recovery of motor function.The key to effective rehabilitation is to give patients greater motor stimulation within their limited range of activities. As a passive training method, whole-body vibration training (WBVT) involves the generation of mechanical waves through a training platform to stimulate muscle vibration and neuromuscular regulation and adaptation. It has also been found to effectively improve the lower-limb muscle strength, spasm, walking ability, and balance of many people, including stroke patients.	3

Background and rationale: choice of comparators	#6b		
Objectives	#7	We aim to determine the effect of 12 weeks of WBVT on stroke patients' lower-limb motor function and neural plasticity, and explore the difference between wbvt and routine rehabilitation training after 6 and 12 weeks of training. In addition, we will evaluate and compare it after 4 and 8 weeks of stopping training. We will also assess the feasibility of a future full-scale RCT.	6
Trial design	#8	This study was designed as a prospective single-blind RCT. Eligible participants with stroke will be assigned randomly to the whole-body vibration training group (WBVG), routine rehabilitation training group (RRTG), and control group (CG) at a ratio of 1:1:1. The WBVG and RRTG will receive exercise interventions in the Sports Laboratory of Shanghai University of Sport, Shanghai, China. The CG will maintain their routine daily lives. The interventions will be implemented 5 times a week for 12 weeks. Participants will be evaluated at baseline, after 6 and 12 weeks of intervention, and 4 and 8 weeks after intervention termination	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Shanghai university of sport,Shanghai,China	
Eligibility criteria	#10	1)clinical diagnosis of first ischemic or hemorrhagic stroke, 2) Montreal Cognitive Assessment (MoCA) score > 20, 3) Brunnstrom stage III or IV, 4) ability to stand and walk without the help of another person, 5) stable medical condition, and 6) duration of illness ≥ 6 months	7
Interventions: description	#11a	**Table 2.** Vibration training schedule **Table 3.** Routine rehabilitation training **Table 5.** Intervention overview	8

Interventions: modifications	#11b	**Table 5.** Intervention overview	10
Interventions: adherance	#11c	**Table 5.** Intervention overview	10
Interventions: concomitant care	#11d	**Table 5.** Intervention overview	10
Outcomes	#12	**Neural plasticity:**MEP amplitude,Short-interval intracortical inhibition（SICI）,M1–pre-SMA connectivity **Lower-limb motor function:**Peak torque,Brunnstrom stage,Fugl-Meyer assessment,Timed up-and-go test,Berg balance test,36-item Short Form Survey	12
Participant timeline	#13	This study was designed as a prospective single-blind RCT. Eligible participants with stroke will be assigned randomly to the whole-body vibration training group (WBVG), routine rehabilitation training group (RRTG), and control group (CG) at a ratio of 1:1:1. The WBVG and RRTG will receive exercise interventions in the Sports Laboratory of Shanghai University of Sport, Shanghai, China. The CG will maintain their routine daily lives. The interventions will be implemented 5 times a week for	6

		12 weeks. Participants will be evaluated at baseline, after 6 and 12 weeks of intervention, and 4 and 8 weeks after intervention termination	
Sample size	#14	The sample size has been estimated using the G*power statistical software (version 3.1.9.2 for Windows 7 X64; Franz Faul, Kiel University, Germany), used widely for this purpose. In this part of the study, the sample size was estimated by F tests: analysis of variance (ANOVA): related measures, between factors: computer required sample size. Under the significance level of 0.05 and repeated-measures ANOVA setting of 80% efficacy, the total number of subjects needed was determined to be 42 (14 per group). Considering a 20% loss rate, we plan to recruit 60 subjects (20 per group).	8
Recruitment	#15	Participants in Shanghai will be recruited through community outreach, from outpatient clinics, with media advertising, and by telephone. All participants will follow their routine medication and physical therapy/massage regimens during the study period	7
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	This study was designed as a prospective single-blind RCT. Eligible participants with stroke will be assigned randomly to the whole-body vibration training group (WBVG), routine rehabilitation training group (RRTG), and control group (CG) at a ratio of 1:1:1. The WBVG and RRTG will receive exercise interventions in the Sports Laboratory of Shanghai University of Sport, Shanghai, China. The CG will maintain their routine daily lives.Numbers (1–60) will be assigned to the participants according to their recruitment times in an Excel software database, and then a random sequence will be generated using the "= rand ()" formula. This sequence will be sorted to allocate the participants to the study groups.	8
Allocation concealment mechanism	#16b	This study was designed as a prospective single-blind RCT. Eligible participants with stroke will be assigned randomly to the whole-body vibration training group (WBVG), routine rehabilitation training group (RRTG), and control group (CG) at a	8

		ratio of 1:1:1. The WBVG and RRTG will receive exercise interventions in the Sports Laboratory of Shanghai University of Sport, Shanghai, China. The CG will maintain their routine daily lives.Numbers (1–60) will be assigned to the participants according to their recruitment times in an Excel software database, and then a random sequence will be generated using the "= rand ()" formula. This sequence will be sorted to allocate the participants to the study groups.	
Allocation: implementation	#16c		
Blinding (masking)	#17a	The data is analyzed by specialized PhD students, they analyse the data be blind to group allocation.	
Blinding (masking): emergency unblinding	#17b	After the results are processed, the grouping can be announced	
Methods: Data collection, management, and analysis			
Data collection plan	#18a	The data is analyzed by specialized PhD students	
Data collection plan: retention	#18b		
Data management	#19	The data is analyzed by specialized PhD students	
Statistics: outcomes	#20a	The statistical analysis will be performed by designated members of the research group who will be blinded to participants' group allocations. All statistical analyses will be conducted using IBM SPSS 24.0. All quantitative data will be summarized and presented using appropriate descriptive statistics, and baseline data from the WBVG， RRTG and CG will be analyzed using the independent-samples *t* test. To explore the effects of the training interventions on stroke patients' motor function and neural	14

		plasticity, repeated-measures analysis of variance will be used to examine differences in outcomes between and within groups at all assessment timepoints	
Statistics: additional analyses	#20b		
Statistics: analysis population and missing data	#20c		
Methods: Monitoring			
Data monitoring: formal committee	#21a	The data is analyzed by specialized PhD students, they analyse the data be blind to group allocation.	
Data monitoring: interim analysis	#21b		
Harms	#22	In the Participants gave an informed consent form	
Auditing	#23	In the Participants gave an informed consent form	
Ethics and dissemination			
Research ethics approval	#24	This study has been approved by the Shanghai University of Sport Research Ethics Committee (102772021RT067)	3
Protocol amendments	#25	Upload as attachment	
Consent or assent	#26a	PhD students in charge of data collection will collect data within the TMS and lower limbs function will be conducted before the intervention as well as at 6 weeks, 12 weeks, and 4 weeks and 8weeks after the intervention	
Consent or assent:	#26b		

ancillary studies		
Confidentiality	#27	Professor Wu, who is in charge of recruitment, completes the participant information management.
Declaration of interests	#28	The authors have no conflicts of interest to declare
Data access	#29	The result will be made public by the person in charge of the Research supported by The Program for Overseas High-level talents at Shanghai Institutions of Higher Learning (TP2020063)
Ancillary and post trial care	#30	In the Participants gave an informed consent form.
Dissemination policy: trial results	#31a	This study has been registered prospectively in the Chinese Clinical Trail Registry(ChiCTR2200055143,1 January 2022).It will be published in accordance with the standards of the Chinese Clinical Trial Registry
Dissemination policy: authorship	#31b	It will be written in accordance with the standards of the Chinese Clinical Trial Registry.
Dissemination policy: reproducible research	#31c	It can be viewed in the Chinese Clinical Trial Registry.
Appendices		
Informed consent materials	#32	Upload as attachment.
Biological specimens	#33	None

None The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist can be completed online using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai